CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-112

STATISTICAL REVIEW(S)

JAN 19 2000

STATISTICAL/CLINICAL REVIEW AND EVALUATION.

NDA#: 21-112

Applicant: Hill Dermaceuticals, Inc.

Name of Drug: ——— Cream

Documents Reviewed: Volumes 1.1, 1.6, and 1.7, dated 3/23/1999

Type of Report: NDA review

Indication: Treatment of cutaneous melanosis

Medical officer: Hon-Sum Ko, M.D. (HFD-540)

INTRODUCTION

The sponsor submitted reports of two Phase 3 studies, East and West, to support the claim of the safety and efficacy of ——— cream in the treatment of patients with cutaneous melanosis (CM). The objective of these studies is to demonstrate that ——— (tretionoin/ hydroquinone/fluocinolone), administered QD for 8 weeks, is safe and effective in the treatment of CM compared to the three possible pair-wise combinations of its components: tretionoin + fluocinolone, tretinoin + hydroquinone, and fluocinolone + hydroquinone in the same vehicle. Both East and West Studies had identical protocol (Protocol No. 24). Throughout this review the abbreviations T, H, and F will be used for individual components tretionoin, hydroquinone, and fluocinolone. Abbreviations THR, TH, FT, and HF will be used for the combinations ——— tretinoin + hydroquinone, tretionoin + fluocinolone, and fluocinolone + hydroquinone.

DESIGN (according to the sponsor's protocol)

Each study was a multicenter, randomized, double-blind, four-arm, parallel-group study. Outpatients 18 year or older with a clinical diagnosis of CM on the face and neck were randomly assigned to one of the four treatment groups: ——— (THR), tretinoin + hydroquinone (TH), tretinoin + fluocinolone (FT), and fluocinolone + hidroquinone (FH). Treatment was applied once daily and continued for 8 weeks. Studies were performed in two geographic areas (East and West). East study included Sites #1 (Dr. Torok, N=100), #2 (Dr. Willis, N=80), and #5 (Dr. Brody, N=22). West study included Sites #3 (Dr. Kelly, N=120) and #4 (Dr. Wieder, N=55). The baseline visit was Day 1. Patients were randomized at Day 1 and were assessed weekly for efficacy and safety.

Primary efficacy variable:

The primary efficacy variable was the proportion of patients with a hyper pigmentation score = 0 (patient cleared) at week 8. Hyper pigmentation was evaluated on a 4-point scale:
0 = none, 1 = mild, 2 = moderate, and 3 = severe.

Secondary efficacy variable:

The secondary efficacy variable in this review was the proportion of patients who had Physician's Global Evaluation of "Cleared" (100% improvement) at week 8. Physician's Global Evaluation was based on a 6-point scale:

0 = cleared (100% improvement),
1 = excellent (75% to < 100% clinical improvement),
2 = good (50% to < 75% clinical improvement),
3 = fair (25% to < 50% clinical improvement),
4 = slight (Less than 25% improvement),
5 = no change.

Reviewer's Comments:

1. ***Randomization.*** *According to Protocol 24, (Volume 1.6, page 70100), "Hill Dermaceutical will randomly assign numbers to the 4 treatment arms. The number assignment of test materials will be chosen by lottery". According to the Full Report of Study No. 24 (Volume 1.6, page 70058), "The sponsor company randomly assigned numbers from 1 to 120 to four different treatment groups. Number assignment was made by lottery." However, the stated randomization procedure of random assignment by lottery was not observed by the sponsor (see Appendix or Volume 1.6, page 70199). The randomization scheme in the East and West studies (see Protocol No. 24) is not valid for the following reasons:*
   a) *Each of the five sites had the same randomization scheme instead of having a separate scheme (see ICH E9 Document).*
   b) *As can be seen from the listing in the Appendix, the first 10 enrolled patients were to be assigned to THR arm. The next 24 patients (from 11 to 34) were to be assigned to dyads only. This scheme is not random and it does not agree with Protocol #24 or the Study Report.*

2. ***Coding of test drugs*** *in the West and East studies was not ensured properly. The tubes of the study drugs were color-coded. The Division of Scientific Investigations (DSI) found that Dr. Torok was able to tell which treatment a patient was getting by the color on the crimp of the tube used. Dr. Torok had the key of the color written on the case report form (see DSI report).*

3. ***Unblinding.*** *The protocol allowed opening the master key envelope for unblinding when a patient achieved clearing of hyper-pigmentation, so that the patient might go to the open phase of the dose-decreasing regimen. Allowing the master key envelope to be opened before the end*

of the double-blind phase made it possible for total unblinding of the whole site.

4. ***Enrollment criteria violations.*** *Certain baseline criteria were not entered into some of the case report forms at Dr. Willis's and Dr. Brody's sites. For instance, patients were required to have stable hyper pigmentation for 3 months prior to entry, and to have skin types II or III. Dr. Brody's site did not have skin type information. Also, some of Dr. Willis's patients (e.g. patients # 24, 56, 59, and 61) did not have information on duration of hyper pigmentation. In addition, some of Dr. Willis's patients did not have any lesions on the dermogram at baseline (patients # 7, 8, 39, and 44). For this reason it would be unclear whether these patients fit the target population intended for labeling.*

5. ***Dropouts.*** *The majority (55%) of Dr. Brody's patients dropped out (11 of the 12 dropouts with unknown reason, just labeled lost to follow-up). The sponsor extrapolated the results for the remaining minority of Dr. Brody's patients to the entire site #5. This reviewer feels that it may be unwise to extrapolate data from the minority of patients to the entire site.*

6. ***Adverse event reporting.*** *The sponsor excluded Dr. Willis site from the safety analysis, because the safety data from this site was considered unreliable. Dr. Willis did not document anticipated adverse effects from the study medications as adverse events.*

7. ***Questionable data documentation.*** *None of Dr. Willis 80 patients reported use of medications within 2 weeks of entry or were documented to be using any concomitant medications.*

8. ***Ambiguity of hyper pigmentation score system.*** *The scoring system (0-3) has overlapping descriptors that make interpretation difficult.*

Statistical methods:

According to the protocol, the primary efficacy population was the ITT population with the LOCF procedure. The ITT population included all enrolled subjects who received at least one application of study drug. The secondary efficacy population was Evaluable population that consisted of all patients who did not violate the protocol and had completed the 8 weeks of study or cleared (hyper pigmentation score of zero) prior to completion of the 8 weeks of treatment.

Reviewer' Comments:

1. *In the East Study, 16 patients of Drs. Willis and Brody (Sites #2 and #5, respectively), and all 100 patients of Dr Torok (Site # 1) had serious protocol violation. The reviewing medical officer (RMO) and the Division of Scientific Investigations (DSI) felt that these 116 patients should be excluded from the East Study. Therefore, in the primary efficacy analysis of the East Study, this reviewer used the Reviewer's Efficacy population excluding those 116 patients.*

2. *In the West Study, the RMO found that 47 patients enrolled in the West study had serious protocol violations and should be excluded from the West Study. Therefore, in the primary*

efficacy analysis of the West Study, the reviewer used a Reviewer's Efficacy population excluding those 47 patients.

3. *In the West study, 41 (34%) of the 120 enrolled patients in Site # 3 (Dr. Kelly) had serious protocol violations. The reviewing medical officer felt that the entire site # 3 should be excluded. Therefore, this reviewer performed an alternative efficacy analysis in the single Site # 4 (Dr. Wieder) of West Study excluding Site #3 (Dr. Kelly).*

Patients age was compared using ANOVA model with the investigator, treatment and investigator-by-treatment effects. Gender and race were compared with the Chi-Square test. The primary efficacy variable was the proportion of subjects with a hyper pigmentation score of 0 at week 8. The difference between treatment groups relative to the primary efficacy variable was estimated using the CMH test adjusting for center. This reviewer chose the proportion of patients who had Physician's Global Evaluation of "Cleared" at week 8 as the secondary efficacy variable. The comparisons of interest were:

THR vs. TH,
THR vs. FT, and
THR vs. HF.

RESULTS OF THE EAST STUDY

Of the 202 subjects who were enrolled in the East Study, 29 (14%) did not complete the study. The reviewing medical officer (RMO) and the Division of Scientific Investigations (DSI) felt that 116 patients enrolled in the East study should not be included in the efficacy analysis. Therefore, in the primary efficacy analysis, this reviewer used the Reviewer's Efficacy population excluding those 116 patients. The sponsor's results for all 202 patients in the ITT population cannot be considered valid and, therefore, are not presented in this review. Table 1 summarizes the subject disposition in the East Study.

There were no significant differences between the treatment groups relative to age (p=0.3), gender (p=0.6), race (p=0.65) and skin type (p=0.7).

Table 1. Subject Disposition in East Study.

Subject Parameter	Treatment	Torok	Willis	Brody	East Study
Enrolled	THR	25	20	9	54
	TH	25	20	5	50
	FT	25	20	5	50
	HF	25	20	3	48
Total		100	80	22	202
Did not complete study	THR	2	1	3	6
	TH	3	3	4	10
	FT	3	1	4	8
	HF	3	1	1	5
Total		11	6	12	29
Reasons for dropout					
Lost to Follow up		6	0	11	17
Pt withdrew		4	0	0	4
Adverse event		1	6	1	8
Protocol Deviation		0	0	0	0
Other		0	0	0	0
Total		11	6	12	29
Sponsor's ITT analysis population		25	20	9	
	THR				54
	TH	25	20	5	50
	FT	25	20	5	50
	HF	25	20	3	48
Total		100	80	22	202
Reviewer's primary efficacy population			17	7	
(116 patients are excluded)	THR				24
	TH		17	3	20
	FT		20	3	23
	HF		16	3	19
Total			70	16	86

Primary Efficacy Analysis in the East Study

The primary efficacy population in this review was the Reviewer's Efficacy population. The primary efficacy variable was the proportion of patients with the hyper pigmentation score of 0 (Cleared) at Week 8. Table 2 shows the primary efficacy analysis in the Reviewer's Efficacy population of the East Study excluding 16 patients of Drs. Willis and Brody (Sites #2 and #5, respectively), and all 100 patients of Dr. Torok (Site # 1).

In the CMH test adjusted for investigator, the proportion of patients who were cleared by Week 8 in the THR group was statistically significantly higher than in the FT group (p=0.005) and only

marginally significantly better than in the TH group (p=0.046). There was no statistically significant difference between the THR and HF groups (p=0.055).

In the Chi-Square test, the proportion of patients who were cleared by Week 8 in the THR group was statistically significantly higher than in the FT group (p=0.033). There was no statistically significant difference between the THR and HF or TH groups (p≥0.16).

Table 2. Primary efficacy analysis in the East Study (16 patients of Drs. Willis and Brody and all 100 patients of Dr. Torok are excluded).
Proportion of Subjects with the Hyper Pigmentation Score = 0 (Cleared) by Week 8.

	Number (%) of subjects cleared at week 8			
	THR	TH	FT	HF
N	24	20	23	19
Yes	6 (25.0%)	1 (5.0%)	0 (0.0%)	1 (5.3%)
No	18 (75.0%)	19 (95.0%)	23 (100.0%)	18 (94.7%)
P-value, CMH test		0.046	0.005	0.055
P-value, Chi-Square test		0.16	0.033	0.19

Secondary efficacy analysis in the East Study

As a secondary efficacy variable, this reviewer chose proportion of patients with the Physician's Global Assessment of "Cleared". Table 3 presents the results for the secondary efficacy variable, proportion of patients rated as "Cleared" by the Physician's Global assessment at Week 8 in the East Study (16 patients of Dr. Willis and Dr. Brody, and all 100 patients of Dr. Torok are excluded).

In the CMH test adjusting for investigator, the proportion of subjects who were rated "Cleared" at week 8 in the THR group was significantly higher than in the FT and HF treatment groups (p≤0.012) and only numerically higher than in the TH group (p=0.054).

In the Chi-Square test, the proportion of subjects who were rated "Cleared" at week 8 in the THR group was significantly higher than in the FT and HF treatment groups (p≤0.036) and only numerically higher than in the TH group (p=0.127).

Table 3. Secondary efficacy analysis in the East Study (16 patients of Drs. Willis and Brody and all patients of Dr.Torok are excluded).
Proportion of Subjects Rated as "Cleared" at Week 8 in the Physician's Global Assessment.

	Number (%) of subjects cleared at week 8			
	THR	TH	FT	HF
N	17	15	19	15
Yes	6 (35.3%)	1 (6.7%)	0 (0.0%)	0 (0.0%)
No	11 (64.7%)	14 (93.3%)	19 (100.0%)	15 (100.0%)
P-value, CMH test		0.054	0.005	0.012
P-value, Chi-Square test		0.127	0.017	0.036

RESULTS OF THE WEST STUDY

Of the 175 subjects who were enrolled in the West Study, 47 (27%) did not complete the study. Table 4 summarizes the subject disposition in the West Study. The reviewing medical officer (RMO) felt that 47 patients enrolled in the West study had serious protocol deviations and should be excluded from the West study. Therefore, for the primary efficacy analysis, the reviewer used the Reviewer Efficacy population excluding those 47 patients. The sponsor's analysis was considered invalid by the RMO and is not shown in this review.

There were no significant differences between the treatment groups relative to age (p=0.76), gender (p=0.88), race (p=0.83) and skin type (p=0.64).

Table 4. Subject Disposition in West Study.

Subject Parameter	Treatment	Kelly	Wieder	West Study
Enrolled	THR	30	15	45
	RA+HQ	30	13	43
	RA+FA	30	14	44
	FA+HQ	30	13	43
Total		120	55	175
Did not complete study	THR	6	3	9
	RA+HQ	16	1	17
	RA+FA	11	2	13
	FA+HQ	7	1	8
Total		40	7	47
Reasons for dropout				
Lost to Follow up		28	2	30
Pt withdrew		0	0	0
Adverse event		1	3	4
Protocol Deviation		2	2	4
Other		9	0	9
Total		40	7	47
Sponsor's ITT population	THR	29	15	44
	RA+HQ	28	13	41
	RA+FA	27	14	41
	FA+HQ	27	13	40
Total		111	55	166
Reviewer primary efficacy Population (47 patients are excluded)	THR	20	14	34
	RA+HQ	19	11	30
	RA+FA	21	12	33
	FA+HQ	18	13	31
Total		78	50	128

Primary Efficacy Analysis in the West Study

Forty-seven (47) subjects enrolled in the West Study took concomitant medications or had other serious protocol deviations. The RMO suggested exclusion of these 47 subjects from the primary efficacy analysis. In this review, the primary efficacy population was the Reviewer's Efficacy population excluding those 47 patients. Table 4 presents the reviewer's analysis for the primary efficacy variable, proportion of patients with the hyper pigmentation score = 0 (Cleared) by Week 8 in the Reviewer's Efficacy population of the West Study.

In the CMH test adjusting for investigator, the proportion of subjects who were cleared by Week 8 in the THR group was significantly higher than in the FT group (p=0.013). However, the proportion

of subjects cleared by Week 8 in the THR group was only numerically higher than in the TH group (p=0.20) and in the HF group (p=0.17).

In the Chi-Square test, the proportion of subjects who were cleared by Week 8 in the THR group was significantly higher than in the FT group (p=0.036). However, the proportion of subjects cleared by Week 8 in the THR group was only numerically higher than in the TH group (p=0.34) and in the HF group (p=0.32).

Table 4. Reviewer's primary efficacy analysis in the West Study: Proportion of Subjects with the Hyper Pigmentation Score = 0 (Cleared) by Week 8. (47 patients with serious protocol deviations are excluded)

	Number (%) of subjects cleared at week 8			
	THR	TH	FT	HF
N	34	30	33	31
Yes	6 (17.7%)	2 (6.7%)	0 (0.0%)	2 (6.5%)
No	28 (82.4%)	28 (93.3%)	33 (100.0%)	29 (93.6%)
P-value in the CMH test		0.20	0.013	0.17
Chi-Square test		0.34	0.036	0.32

Secondary efficacy analysis in the West Study

This reviewer chose the proportion of patients with the Physician's Global Assessment of "Cleared" as the secondary efficacy variable. Table 5 presents the results for the secondary efficacy variable, proportion of patients rated as "Cleared" by the Physician's Global assessment at Week 8 in the West Study (47 patients with the protocol violations are excluded).

In the CMH test adjusting for investigator, the proportion of subjects who were rated "Cleared" at Week 8 in the THR group was statistically significantly higher than in the FT group (p=0.036). However, the proportion of subjects who were rated "Cleared" at Week 8 in the THR group was only numerically higher than in the TH group (p=0.51) and in the HF group (p=0.26).

In the Chi-Square test, the proportion of subjects who were rated "Cleared" at Week 8 in the THR group was only numerically higher than in the FT group (p=0.094), in the TH group (p=0.79) and in the HF group (p=0.48).

Table 5. Secondary efficacy analysis in the West Study (47 patients are excluded). Proportion of Subjects Rated as "Cleared" at Week 8 in the Physician's Global Assessment.				
	Number (%) of subjects cleared at week 8			
	THR	TH	FT	HF
N	31	21	26	29
Yes	5 (16.1%)	2 (9.5%)	0 (0.0%)	2 (6.9%)
No	26 (83.9%)	19 (90.5%)	26 (100.0%)	27 (93.1%)
P-value, CMH test		0.51	0.036	0.26
P-value, Chi-Square test		0.79	0.094	0.48

Alternative Efficacy analysis in the single Site # 4 (Dr.Wieder) of West Study with Site #3 (Dr. Kelly) excluded.

Since Site # 3 (Dr. Kelly) had a number of serious problems, the reviewing medical officer felt that the entire site #3 should be excluded. Table 6 presents the alternative analysis for the primary efficacy variable, proportion of patients with the hyper pigmentation score = 0 (Cleared) by Week 8 in the single site # 4 (Dr.Wieder) of West Study (Dr. Kelly is excluded). In the Fisher's exact test, there was no statistically significant difference between the THR group and the TH group (p=1.0), FT group (p=0.6), or HF group (p=1.0).

Table 6. Alternative primary efficacy analysis in the single site # 4 (Dr.Wieder) of West Study (Dr. Kelly excluded): Proportion of Subjects with the Hyper Pigmentation Score = 0 (Cleared) by Week 8.				
	Number (%) of subjects cleared at week 8			
	THR	TH	FT	HF
N	15	13	14	13
Yes	3 (20.0%)	2 (15.4%)	1 (7.1%)	2 (15.4%)
No	12 (80.0%)	11 (84.6%)	13 (92.9%)	11 (84.6%)
P-value, Fisher's exact test		1.0	0.6	1.0

Table 7 shows the results of the secondary efficacy analysis in the single site #4 (Dr. Wieder only) of the West study (Dr. Kelly's Site #3 excluded). In the Fisher's exact test, proportion of subjects who were rated "Cleared" at Week 8 in the THR group was only numerically higher than in the FT group (p=0.6), and in the HF or TH groups (p=1.0).

Table 7. Alternative secondary efficacy analysis in the Site # 4 (Dr. Wieder) of West Study (Dr. Kelly excluded).
Proportion of Subjects Rated as "Cleared" at Week 8 in the Physician's Global Assessment.

	Number (%) of subjects cleared at week 8			
	THR	TH	FT	HF
N	14	12	13	12
Yes	3 (21.4%)	2 (16.7%)	1 (7.7%)	2 (16.7%)
No	11 (78.6%)	10 (83.3%)	12 (92.3%)	10 (83.3%)
P-value, Fisher's exact test		1.0	0.6	1.0

Integrated Safety of the East and West Studies

Reviewer's Comments:

1. ***In this NDA submission, only 99 patients were exposed to the THR treatment. Integrated safety information is available only for 79 THR patients. This is far short of the number of exposed patients recommended for safety analysis by the ICH Document.***

2. ***According to the Study Report (Volume 1.6, page 70082), all 377 patients enrolled in the East and West studies were given the study treatments and "all patients that were entered in the treatments were analyzed for safety". However, the safety summary tables on pages 70030, 70031, 70082, and 70083 of Volume 1.6, provide analysis of adverse events for only 297 (78.8%) of the 377 treated patients. . The sponsor excluded Dr. Willis's site from the safety analysis, because the safety data from this site was considered unreliable. Dr. Willis did not document anticipated adverse effects from the study medications as adverse events.***

For the available safety information, Table 8 shows the number and percent of patients with adverse events in the East and West studies combined. The THR group had significantly higher percentage of patients with adverse events than the HF group (p=0.001).

Table 8. Number (percent) of patients with adverse events at Week 8 in the West and East Studies combined

	THR	TH	FT	HF
N	79	73	74	71
Number (%) of patients with adverse events	36 (45.6 %)	29 (39.7 %)	22 (29.7%)	9 (12.7%)
P-value, Chi-Square test		0.57	0.064	0.001

REVIEWER'S CONCLUSIONS (which may be conveyed to the sponsor):

The sponsor did not attend the End-of-Phase 2 meeting to receive FDA guidance on the Phase 3 protocol. The Phase 3 Protocol No. 24 for the East and West Studies has a number of serious

deficiencies (see Reviewer's Comments on pages 2-3). The randomization scheme in the Protocol No. 24 (See Appendix or Volume 1.6, page 70199) is not valid for the following reasons:

1. Each of the five sites had the same randomization scheme instead of having a separate scheme (see ICH E9 Document).
2. As can be seen from the randomization listing, the first 10 enrolled patients were to be assigned to the THR arm. The next 24 patients (from #11 to #34) were to be assigned to dyads only. With this scheme, the allocation of patents to treatment arms cannot be considered random. The validity of statistical inferences is based on random allocation to treatments. With the allocation scheme used, it is difficult to draw a scientific conclusion concerning the efficacy results from these studies.

In addition, study sites had serious protocol violations (see Reviewer's Comments on pages 2-3). Following the recommendations of the Reviewing Medical Officer and the Division of Scientific Investigations, for the primary efficacy analysis in the East Study, this reviewer excluded 16 patients of Drs. Willis and Brody (Sites #2 and #5, respectively), and all 100 patients of Dr Torok (Site # 1). For the primary efficacy analysis in the West Study, this reviewer excluded 47 patients of Drs. Kelly and Wieder (Sites 3 and 4, respectively). For alternative analysis, this reviewer used the single site # 4 (Dr. Wieder) of West Study (excluding Dr. Kelly). The primary efficacy variable was the proportion of patients with the hyper pigmentation score of 0 (Cleared) at Week 8.

Efficacy results

The primary efficacy analysis in the East Study shows that the proportion of subjects who were cleared by Week 8 in the THR group was statistically significantly higher than in the FT group ($p=0.005$) and only marginally significantly higher than in the TH group ($p=0.046$). There was no statistically significant difference in the proportion of subjects who were cleared by Week 8 between the THR and HF groups ($p=0.055$).

The primary efficacy analysis in the West Study shows that the proportion of subjects who were cleared by Week 8 in the THR group was statistically significantly higher than in the FT group ($p=0.013$). However, there was no statistically significant difference in the proportion of subjects who were cleared by Week 8 between the THR group and the TH group ($p=0.20$) or the HF group ($p=0.17$).

In the alternative efficacy analysis of the single site # 4 (Dr. Wieder) of West Study, there was no statistically significant difference between the THR group and FT group, TH group, or HF group ($p \geq 0.6$). Secondary efficacy analysis supported the results of the primary efficacy analysis.

Safety

In this NDA submission, only 99 patients were exposed to the THR treatment. Integrated safety information is available only for 79 patients exposed to the THR treatment. This is far short of the number of exposed patients recommended for safety analysis by the ICH Document.

According to the Study Report (Volume 1.6, page 70082), all 377 patients enrolled in the East and West studies were given the study treatments and "all patients that were entered in the treatments were analyzed for safety". However, the safety summary tables in this submission provide analysis of adverse events for only 297 (78.8%) of the 377 treated patients. The sponsor excluded Dr. Willis site from the safety analysis, because the safety data from this site was considered unreliable. Dr. Willis did not document anticipated adverse effects from the study medications as adverse events.

Overall Conclusions:

Randomization scheme in the Phase 3 studies is not valid. The results of the two Phase 3 studies failed to support the claim that [redacted] is statistically significantly superior in efficacy to its components. Safety information for [redacted] is available for only 79 patients which is far short of the number of exposed patients recommended for safety analysis by the ICH Document. This is a matter for the clinical judgement of the reviewing Medical Division to decide whether this application should be approved given the efficacy and safety issues.

/S/ 01.19.2000

Valeria Freidlin, Ph.D.
Mathematical Statistician, Biometrics III

/S/ 1/19/2000

Concur: Mohamed Al-Osh, Ph.D.
Acting Team Leader, Biometrics III

cc:
Archival NDA 21-112
HFD-540
HFD-540/Mr. White
HFD-540/Dr. Wilkin
HFD-540/Dr. Ko
HFD-725/Dr. Huque
HFD-725/Dr. Al-Osh
HFD-725/Dr. Freidlin
HFD-344/Dr. Carreras
Chron. (HFD-725)
This review contains 14 pages and Appendix (one page).
Wordfile' [redacted] 21112_r4\1-19-2000

APPEARS THIS WAY
ON ORIGINAL

STATISTICAL REVIEW AND EVALUATION

Medical Division: Division of Dermatologic/Dental Drug Products (DDDDP, HFD-540)
Biometrics Division: Division of Biometrics III (HFD-725)

DATE REVIEW COMPLETED:	12/15/01
NDA NO.:	21-112/4S
SERIAL NO.:	000
DATE RECEIVED:	07/24/01, 09/24/01, and 11/23/01
DRUG NAME:	Tri-Luma Cream
INDICATION:	Melasma of the face
ROUTE OF ADMINISTRATION:	Topically once daily before bedtime
SPONSOR:	Hill Dermaceuticals, Inc.
DOCUMENTS REVIEWED:	Volumes 1, 31-46 submitted 7/20/01; analyses dated 9/19/01 and 11/22/01
Related INDs, NDAs:	[redacted] NDA 21-112
STATISTICAL REVIEWER:	Shiowjen Lee, Ph.D. (HFD-725)
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Distribution: NDA 21-112/000
HFD-540/Dr. Wilkin
HFD-540/Dr. Ko
HFD-540/Ms. Lutwak
HFD-710/Dr. Anello
HFD-725/Dr. Huque
HFD-725/Dr. Alosh
HFD-725/Dr. Lee

Table of Contents for NDA 21-112

Executive Summary

The study drug product is Tri-Luma, which is a combination of three active ingredients (0.01% fluocinolone acetonide + 0.05% tretinoin + 4.0% hydroquinone). It is indicated for treatment of melasma of the face and designed to be administered once daily before bedtime for 8 weeks.

The new drug application, NDA 21-112, was submitted on 3/19/1999 and was issued a not approvable letter on 1/21/2000. The reasons for not approvable action in Clinical/Statistical section were:

1. Because melasma is often a chronic condition, and because melasma may regress upon discontinuation of therapy with the test drug product, the safety for long-term use should be assessed.
2. A study with adequate sample size should be performed to determine the contact sensitization potential of the test drug product.
3. Studies on systemic absorption and HPA axis function (adrenal suppression) should be provided to support the systemic safety of the test drug product.
4. The contribution of each of the three drug components was assessed by comparing the test drug product with each of three creams that each omitted a different active drug (the three dyads). Superiority of the test drug product over each of the three dyads has not been established. Also, the test drug product appears to offer no compelling advantage over the three dyads in local adverse events.

Sponsor's current submission, an NDA amendment, is a response to the non-approvable letter to NDA 21-112. Six clinical studies, which included two new Phase III pivotal trials (protocols 28A and 28B), and four supportive studies, were completed and submitted in the Statistical section of the current NDA. Two long-term trials (protocols 29 and 30), which were designed as open-label and 12-month studies, are on going. This statistical review primarily addresses Clinical/Statistical request #4 and, consequently, focuses on the efficacy and safety evaluation of the two Phase III pivotal studies (protocols 28A and 28B).

Two pivotal trials were conducted in US between August 2000 and January 2001. Total of 338 and 303 subjects were enrolled from 7 and 6 centers, respectively, for studies 28A and 28B. The enrolled subjects were randomized based on an allocation ratio of 1:1:1:1 to Tri-Luma (TRI), fluocinolone+hydroquinone (FH), fluocinolone+tretionoin (FR), and hydroquinone+tretinoin (HR). This resulted in 85, 85, 85 and 83 subjects in TRI, FH, FR, and HR groups for study 28A; while 76, 76, 76 and 75 subjects were in TRI, FH, FR and HR groups for study 28B. The demographic characteristics of the enrolled patients were:

- Aged between 21 and 74.
- More than 97% of enrolled subjects are females within each study.
- Approximately 70% and 62% of subjects are Caucasians in studies 28A and 28B.
- More than 61% of enrolled subjects were skin type of II or III within each study.

The intent-to-treat (ITT) analysis, treating missing data as failures, showed the superiority of Tri-Luma over each of the three dyads in the primary efficacy endpoint, the proportion of subjects with investigator's assessment of melasma severity score of 0 at Day 56 (p-value < 0.001 and ≤ 0.045 in studies 28A and 28B, respectively).

Having said that the two studies win on the primary efficacy endpoint, this reviewer, however, has the following concern regarding the randomization in the trials:

Randomization: The issue of any selection bias in the efficacy results due to the way of assigning study sites to studies 28A and 28B as well as deviation from pre-planned randomization during the course of the trials is not addressed based on the Sponsor's submission. The Sponsor's assignment of site numbers in each study was not sequential (i.e. odd number sites as one study and even number sites as another study). It is not clear whether such assignment was a post-hoc and if so, the implication on the efficacy results. The Sponsor should provide clarification/justification to address this issue.

Forty-five subjects (15%. See pages 8-2772 – 2775, Volume 40 of the NDA submission) in study 28B used concomitant drug. The Subjects who took excluded concomitant medication did contribute efficacy for Tri-Luma treatment in study 28B. The non-superiority of Tri-Luma to dyads in the primary efficacy endpoint based on the analyses excluding these subjects could be due to the fact that reduced sample sizes are not powered enough to detect the difference between treatments. The medical reviewer should comment on whether such protocol deviation is minor and, consequently, did not significantly affect the evaluation of efficacy or safety of the study drugs. On the other hand, the Sponsor should perform additional analyses to address the issue that no bias involves in the efficacy results due to the concomitant drug usage.

It should be noted that more than 97% of enrolled subjects in studies 28A and 28B are females. Whether female subjects are the primary treated population for melasma indication is a clinical issue and should be commented by the clinical reviewer. Such information should be reflected on the labeling.

Safety assessment based on the extent of exposure to the study drug and the incidence of adverse events from two pivotal trials showed that the short-term safety profile of Tri-Luma treatment generally is acceptable as compared to other dyad groups. The most common adverse events were the application site desquamation and erythema (i.e. 37.9% and 41.0%, respectively). The incidence rates in Tri-Luma group were higher than the two dyad groups, FH and FR, but comparable to HR arm in erythema and lower than HR group in desquamation.

I. Introduction and Background

The study drug product, Tri-Luma (formerly known as ——— in NDA 21-112 previously submitted), is a combination of three active ingredients (0.01% fluocinolone acetonide + 0.05% tretinoin + 4.0% hydroquinone). Each component of the drug product has been studied and used in its individual preparation. Tri-Luma is designed to be administered once daily before bedtime for 8 weeks in the treatment of melasma of the face.

The new drug application, NDA 21-112, was submitted on 3/19/1999 and was issued a not approvable letter on 1/21/2000. The reasons for not approvable action in Clinical/Statistical section were:

1. Because melasma is often a chronic condition, and because melasma may regress upon discontinuation of therapy with the test drug product, the safety for long-term use should be assessed.
2. A study with adequate sample size should be performed to determine the contact sensitization potential of the test drug product.
3. Studies on systemic absorption and HPA axis function (adrenal suppression) should be provided to support the systemic safety of the test drug product.
4. The contribution of each of the three drug components was assessed by comparing the test drug product with each of three creams that each omitted a different active drug (the three dyads). Superiority of the test drug product over each of the three dyads has not been established. Also, the test drug product appears to offer no compelling advantage over the three dyads in local adverse events.

Sponsor's current submission, an NDA amendment, is a response to the non-approvable letter to NDA 21-112. Six clinical studies, which included two new Phase III pivotal trials (protocols 28A and 28B), and four supportive studies, were completed and submitted in the Statistical section of the current NDA (dated 7/20/01). Two long-term trials (protocols 29 ——— ,, which were designed as open-label and 12-month studies, are on going. However, 6-month data from study 29 were submitted (dated 7/20/01). The four supportive studies included one efficacy/safety trial submitted in the previous NDA (study 24), one on adrenal suppression effect of Tri-Luma (study 33), one cumulative irritancy study (study 36), and one on sensitization effect of Tri-Luma (study 37). The Agency made statistical requests concerning their submission on 8/23/01 and 11/16/01 (see Appendix B). The Sponsor submitted their responses dated 9/19/01 and 11/22/01, respectively.

This statistical review will primarily address Clinical/Statistical concern #4 and, consequently, will focus on the efficacy and safety evaluation of the two Phase III pivotal studies (protocols 28A and 28B). The layout of this review is described as follows. Section II summarizes and discusses the efficacy of Tri-Luma in the treatment of melasma indication. In both pivotal trials, the efficacy of Tri-Luma was compared with those of three dyads – fluocinolone+hydroquinone, fluocinolone+tretionoin, and hydroquinone+tretinoin. Section III summarizes the safety assessment of two Phase III studies. The summary and conclusion of the efficacy and safety of Tri-Luma are included in Section IV. Throughout the review, the abbreviations TRI, FH, FR, and HR are used for Tri-Luma, fluocinolone + hydroquinone, fluocinolone + tretinoin, and hydroquinone + tretinoin, respectively.

II. Efficacy Review

Study Design of 28A and 28B:

The studies were identically designed as randomized, investigator-mask, 4-arm, parallel-group and multicenter. Seven and 6 centers were included in studies 28A and 28B, respectively (see Table AII.1 of the Appendix for details). The objective of the studies was to evaluate the safety and efficacy of Tri-Luma in comparison to three dyads in the treatment of melasma of the face.

Subjects who were 18 years of age or older and satisfied the inclusion criteria were admitted to the studies and randomized in a ratio of 1:1:1:1 to receive TRI, FH, FR, and HR treatments. According to the Sponsor, the treatment assignment used a block size of 4 and was based on a computer-generated randomization list prior to the start of the trials. Patient assignment to a treatment group was done in a sequential order of enrollment within center. The enrolled subjects applied medication once daily before bedtime for 8 weeks. Clinical assessment was collected at weeks 1, 2, 4 and 8. The study endpoint was Week 8 (or Day 56).

Population Analyzed in the Protocol/Submission:
Two populations were analyzed in the Sponsor's submission:

- Intent-to-treat (ITT) population: defined as all patients who were randomized to therapy and dispensed the study material. Their primary analysis was based on such population.
- Per-Protocol (PP) population was **re-defined**[1] before the study was unblinded. It included all patients who had at least one study evaluation and at least 4 weeks of treatment.

Missing values were treated as failures for dichotomized endpoints in both populations. All other analyses in both populations were performed on the observed data.

Efficacy Endpoints Specified in the Protocol and Amendments:
The therapeutic effectiveness of Tri-Luma cream was evaluated based on the following efficacy endpoints specified in the protocol:

- Primary: proportion of subjects with treatment success at Day 56, where treatment success was defined as investigator's static assessment of melasma severity score of 0.
- Secondary:
    - Proportion of subjects with investigator's static assessment of melasma severity score of 0 or 1 at Day 56
    - Physician's global improvement from baseline to Day 56
    - Patient's static global assessment at Day 56
    - Physician's static global assessment at Day 56

The Investigator's Static Assessment of Melasma Severity was evaluated at baseline; weeks 1, 2, 4 and 8 based on a 4-point scale:

0 = melasma lesions approximately equivalent to surrounding normal skin or with minimal residual hyperpigmentation
1 = mild (slightly darker than the surrounding normal skin)
2 = moderate (moderately darker than the surrounding normal skin)

[1] The PP population was originally defined in the protocol as "all patients who do not violate the protocol and complete 8 weeks of treatment".

3 = severe (markedly darker than the surrounding normal skin)

The Physican's global improvement from baseline was evaluated by comparing the extent of melasma at each follow-up visit (i.e. weeks 1, 2, 4 and 8) to a full-face photograph taken at baseline according to a 7-point scale:

0 = completely clear; 100% improvement/clearance from baseline;
1 = almost clear; about 90% improvement/clearance from baseline;
2 = significant or marked improvement; about 75% improvement/clearance from baseline
3 = moderate improvement; about 50% improvement/clearance from baseline
4 = slight improvement; about 25% improvement/clearance from baseline
5 = no change from baseline
6 = worse; hyperpigmentation appears darker from initial presentation at baseline

For Physician's Static Global assessment, a 3-point scale was used and was evaluated at Day 56:

0 = completely clear; no evidence of hyperpigmentation
1 = nearly clear; only minor visual evidence of hyperpigmentation
2 = significant evidence of hyperpigmentation

The Patient's Static Global assessment was evaluated at Day 56 based on a 3-point scale:

1 = completely cleared
2 = nearly cleared
3 = significant hyperpigmentation present

Statistical Analysis Plan in the Protocol:

- Cochran-Mantel-Haenszel test adjusting for study site was proposed to analyze the dichotomized endpoints – proportion of subjects with treatment success; and proportion of subjects with static severity score of 0 or 1.
- Rank analysis of variance was proposed to analyze the other secondary efficacy endpoints.

Superiority Criteria:

The primary comparison was Tri-Luma against each of three dyads:

- Tri-Luma vs. FH (fluocinolone + hydroquinone)
- Tri-Luma vs. FR (fluocinolone + tretinoin)
- Tri-Luma vs. HR (hydroquinone + tretinoin)

The criterion for superiority evaluation was that p-value < 0.05 for each comparison.

Reviewer's Comments on Studies 28A and 28B:

1. From statistical point of view, Sponsor's pivotal studies were done in a double-blind manner despite the study report (page 8-0027, Volume 31) indicated "investigator-masked". That is, both investigator and patient parties were not aware of treatment assignment (as indicated in Volume 41, Integrated Summary of Efficacy). The reasons are:
   - Dispensing and collecting of test materials was assigned to a third party that did not have contact with investigators and patients (page 8-3139, Volume 41).
   - Study medication was supplied in identical opaque tubes with blinded labeling (page 8-0026, Volume 31).

2. Sponsor's computer-generated randomization list included 700 numbers (Section 15.1.5, Volume 32). According to the Sponsor's response to this reviewer's request (dated 9/19/01 and 11/22/01), each site was assigned a specified number of patients, 60 per site, and enrolled patients were assigned sequentially within center according to the randomization list. Two phenomena are identified (pages 8-0529 – 8-0545, Volume 32) in their randomization list:
   - Study 28A included sites 1, 3, 5, 7, 9, 11 and 13; while study 28B included sites 2, 4, 6, 8, 10 and 12. It is not clear from the Sponsor's documentation whether the site numbers were assigned prior to initiation of the trials.
   - Neither documentation (at the IND protocol stage) regarding the number of randomization codes assigned to each study site prior to initiation of the trials, nor the deviation in assignment for some study sites (i.e. sites 3, 4, and 12) are provided (see Appendix C for details).

   The issue of any selection bias in the efficacy results due to the way of assigning study sites to studies 28A and 28B as well as deviation from pre-planned randomization during the course of the trials is not addressed based on their submission. The Sponsor's assignment of sites numbers in each study was not sequential. It is not clear whether such assignment was a post-hoc and if so, the implication on the efficacy results. The Sponsor should provide clarification/justification to address the issues, as the validity of statistical analyses relies on appropriate randomization procedure.

3. [redacted]

4. Sponsor's PP analyses in the submission was re-defined before the studies were unblinded. The Division had requested analysis based on the PP population defined originally in the protocol (i.e. all patients who did not violate the protocol and who completed 8 weeks of treatment). The results of PP re-analysis (dated 9/19/01) are consistent. However, both PP analyses included subjects who took medication that should had been excluded, as per the protocol. The impact of these subjects on the efficacy results will be commented later.

5. [redacted]

Efficacy Results:

1. Patient Disposition and Baseline Characteristics

To evaluate the comparability between treatments, Table 1 presents the patient disposition for studies 28A and 28B. Generally, the discontinuation rate was comparable between treatment

groups within each study. The difference between the ITT (enrolled subjects) and PP[2] populations is small and treatment groups were comparable with respect to the PP population as well as subjects who completed studies.

Table 1. Patient Disposition: Studies 28A and 28B

Study 28A	Tri-Luma	fluocinolone +hydroquinone	fluocinolone + tretinoin	hydroquinoe + tretinoin	Total
Entered	85	85	85	83	338
Completed study	81 (95.3%)	81 (95.3%)	79 (92.9%)	76 (91.6%)	317 (93.8%)
Discontinued	4 (4.7%)	4 (4.7%)	6 (7.1%)	7 (8.4%)	21 (6.2%)
Patient request	1 (1.2%)	1 (1.2%)	0	2 (2.4%)	4 (1.2%)
Adverse event	0	0	3 (3.5%)	1 (1.2%)	4 (1.2%)
Lost to follow-up	0	3 (3.5%)	3 (3.5%)	1 (1.2%)	7 (2.1%)
Non-compliance	1 (1.2%)	0	0	1 (1.2%)	2 (0.6%)
Other	2 (2.4%)	0	0	2 (2.4%)	4 (1.2%)
Per-Protocol population	81 (95.3%)	82 (96.5%)	80 (94.1%)	79 (95.2%)	322 (95.3%)
Study 28B	**Tri-Luma**	**fluocinolone +hydroquinone**	**fluocinolone + tretinoin**	**Hydroquinoe + tretinoin**	**Total**
Entered	76	76	76	75	303
Completed study	71 (93.4%)	70 (92.1%)	72 (94.7%)	72 (96.0%)	285 (94.1%)
Discontinued	5 (6.6%)	6 (7.9%)	4 (5.3%)	3 (4.0%)	18 (5.9%)
Patient request	2 (2.6%)	0	1 (1.3%)	1 (1.3%)	4 (1.3%)
Adverse event	0	1 (1.3%)	1 (1.3%)	0	2 (0.7%)
Lost to follow-up	2 (2.6%)	2 (2.6%)	1 (1.3%)	1 (1.3%)	6 (2.0%)
Patient ineligibility	1 (1.3%)	0	0	0	1 (0.3%)
Non-compliance	0	3 (3.9%)	1 (1.3%)	1 (1.3%)	5 (1.7%)
Per-Protocol population	73 (96.1%)	71 (93.4%)	72 (94.7%)	74 (98.7%)	290 (95.7%)

Source: Sponsor's NDA submission (pages 8-0035 – 0036, Volume 31 and pages 8-2071 – 2072, Volume 37).

For the comparison between treatments with respect to demographics and baseline characteristics, Table AII.2 of the Appendix summarizes the results. Generally, no outstanding discrepancies between treatments are identified for each study. However, Tri-Luma group had a higher rate of subjects with moderate melasma severity at baseline than other groups. The difference is significant in study 28A (i.e. 81.2% vs. 65.9%, 74.1% and 61.4% with p-value = 0.015), but not significant in study 28B. The impact of such unbalanced distribution in baseline disease severity status on the efficacy results will be commented in the primary efficacy endpoint section.

It should be noted that a significantly higher proportion of female subjects was enrolled in both studies (i.e. 98.2% and 97.4% in studies 28A and 28B, respectively). Whether female subjects are the primary treated population for this indication is a clinical issue. The clinical reviewer should comment on this issue and such information should be reflected on the labeling.

2. Primary Efficacy Endpoint

In studies 28A and 28B, Tri-Luma treatment demonstrated significantly greater improvement than each of the three dyads over 8-week therapy as assessed by the proportion of subjects with treatment success at Day 56, where treatment success is defined as investigator's static assessment of melasma severity score of 0. Table 2 presents efficacy results of the two studies.

[2] Sponsor's re-defined PP population before un-blinding, i.e. all patients who had at least one study evaluation and at least 4 weeks of treatment.

Results of Table 2 are summarized below:

- The analyses based on ITT and PP populations are consistent.
- In study 28A, Tri-Luma cream demonstrated superiority over each of the three dyads as p-value for each comparison is < 0.001.
- Similarly in study 28B, Tri-Luma cream is superior to each of the three dyads in the proportion of subjects with treatment success (p-value ≤ 0.045).
- Two trials showed study variability, as the success rates in study 28A are approximately 3-time of those in study 28B.

Table 2: Proportion of Subjects with Melasma Severity Score of 0 at Day 56

SUTDY 28A	TRI (n=85)	FH (n=85)	FR (n=85)	HR (n=83)	Comparison	p-value
ITT analysis n (%)	32 (37.6%)	3 (3.5%)	0	12 (14.5%)	TRI vs. FH TRI vs. FR TRI vs. HR	< 0.001 < 0.001 < 0.001
PP analysis n/N (%)	32/81 (39.5%)	3/82 (3.7%)	0/80 (0%)	12/79 (15.2%)	TRI vs. FH TRI vs. FR TRI vs. HR	< 0.001 < 0.001 < 0.001
STUDY 28B	**TRI (n=76)**	**FH (n=76)**	**FR (n=76)**	**HR (n=75)**	**Comparison**	**p-value**
ITT analysis n (%)	10 (13.2%)	1 (1.3%)	3 (3.9%)	3 (4.0%)	TRI vs. FH TRI vs. FR TRI vs. HR	0.005 0.042 0.045
PP analysis n/N (%)	10/73 (13.7%)	1/71 (1.4%)	3/72 (4.2%)	3/74 (4.1%)	TRI vs. FH TRI vs. FR TRI vs. HR	0.006 0.039 0.040

Source: Sponsor's NDA submission (pages 8-0039 and 8-0096, Volume 31 and pages 8-2075 and 8-2126, Volume 37)

Discussion:

(a) As commented earlier, Tri-Luma group had a higher rate of subjects with moderate melasma severity at baseline as compared with other treatment groups within each study. The difference is significant in study 28A (i.e. 81.2% vs. 65.9%, 74.1% and 61.4% with p-value = 0.015), but not significant in study 28B. Consequently, an issue about whether the success rate at Day 56 depending upon the baseline disease status is raised. This is addressed as follows.

The efficacy results in investigator's assessment of melasma severity at Day 56 by baseline melasma severity are presented in Table AII.3 of the Appendix:

- For study 28A, Tri-Luma treatment has numerically higher proportions of subjects with treatment success (i.e. severity score of 0) at Day 56, regardless of the disease severity status at baseline (see Table AII.3). Furthermore, this reviewer performed a sensitivity analysis for study 28A assuming the same rates of disease severity at baseline for all treatment arms (i.e. Tri-Luma and the three dyads). The results were consistent.
- For study 28B, a higher percentage of subjects in Tri-Luma group, who had moderate disease severity at baseline, achieved treatment success at Day 56. For subjects with severe baseline disease status, Tri-Luma group is slightly more effective than FH and FR groups, but same as HR group (1.3% vs. 1.3%) in achieving treatment success (see Table AII.3).

Therefore, it can be concluded that Tri-Luma treatment is overall more effective than each of the three dyads with respect to the proportion of subjects achieving treatment success.

(b) As indicated in the reviewer's comments, the assignment of study sites was not sequential. This reviewer performed some sensitivity analyses of study-site assignment. The results are summarized in Table AII.4 of the Appendix. One analysis (Table AII.4 (a)) categorized study sites 1-7 as one study, and other sites as another study. The conclusion is consistent. The other analysis (Table AII.4 (b)), which is rather an extreme case, categorized study sites with the best 7 Tri-Luma response rates as one study, and other sites as another study. The results showed non-significant results for the comparisons of TRI vs. FR and HR (p-value = 0.097 and 0.106).

3. Secondary Efficacy Endpoints

Four secondary efficacy endpoints in the protocol were:

- Proportion of subjects with investigator's assessment of severity score of 0 or 1
- Physician's assessment of global improvement from baseline
- Patient's static global assessment
- Physician's static global assessment

Results of the two studies in the proportion of subjects with severity score of 0 or 1 are summarized in Table 3. Both studies showed that Tri-Luma cream is superior to each of the three dyads (p-value < 0.001).

Table 3: Proportion of Subjects with Severity Score of 0 or 1 at Day 56: ITT Analysis

SUTDY 28A	**TRI (n=85)**	**FH (n=85)**	**FR (n=85)**	**HR (n=83)**	**Comparison**	**p-value**
	73 (85.9%)	42 (49.4%)	23 (27.1%)	51 (61.4%)	TRI vs. FH TRI vs. FR TRI vs. HR	< 0.001 < 0.001 < 0.001
STUDY 28B	**TRI (n=76)**	**FH (n=76)**	**FR (n=76)**	**HR (n=75)**	**Comparison**	**p-value**
	51 (67.1%)	26 (34.2%)	21 (27.6%)	23 (30.7%)	TRI vs. FH TRI vs. FR TRI vs. HR	< 0.001 < 0.001 < 0.001

Source: Sponsor's NDA submission (page 8-0041, Volume 31 and page 8-2077, Volume 37)

described below:

- For Physician's Assessment of Global Improvement from baseline, define success *as "global improvement of 100%"* and failure as others. For missing data in the ITT population, they are treated as failures.
- For Physician's Static Global and Patient's Static Global, define success as "*completely cleared*"; and failure as others. Similarly, the missing data in the ITT population are treated as failures.

The efficacy results are presented in Tables 4, 5 and 6, respectively:

- For the proportion of patients with physician's global improvement of 100% from baseline, Tri-Luma cream showed superiority to each of the three dyads as p-value $\leq$ 0.020 and $\leq$ 0.045 in studies 28A and 28B, respectively (Table 4).

- For the proportion of subjects with Patient's Static Global assessment rated as "completely cleared", Tri-Luma treatment demonstrated superiority over FH and FR groups, but ***not*** over HR arm. This is because p-value = 0.071 and 0.301 for the comparison between Tri-Luma and HR group in studies 28A and 28B, respectively (Table 5).
- For the proportion of subjects with Physician's Static Global rated as "completely cleared", Tri-Luma cream was significantly more effective than each of the three dyads (p-value $\leq$ 0.009 and $\leq$ 0.027, respectively, in studies 28A and 28B, Table 6).

Table 4: Physician's Assessment for Global Improvement at Day 56: ITT Analysis

	STUDY 28A				[1] Dichotomization analysis	
Global improvement	**TRI (n=85)**	**FH (n=85)**	**FR (n=85)**	**HR (n=83)**	**Comparison**	**p-value**
100%	22 (25.9%)	2 (2.4%)	0	11 (13.3%)	TRI vs. FH	< 0.001
90%	22 (25.9%)	11 (12.9%)	2 (2.4%)	20 (24.1%)	TRI vs. FR	< 0.001
75%	17 (20.0%)	12 (14.1%)	6 (7.1%)	13 (15.7%)	TRI vs. HR	0.020
50%	15 (17.6%)	25 (29.4%)	16 (18.8%)	21 (25.3%)		
25%	4 (4.7%)	19 (22.4%)	36 (42.4%)	9 (10.8%)		
No change	1 (1.2%)	11 (12.9%)	17 (20.0%)	5 (6.0%)		
Worse	0	2 (2.4%)	3 (3.5%)	1 (1.2%)		
Missing	4 (4.7%)	3 (3.5%)	5 (5.9%)	3 (3.6%)		
	STUDY 28B				[1] **Dichotomization analysis**	
Global improvement	**TRI (n=76)**	**FH (n=76)**	**FR (n=76)**	**HR (n=75)**	**Comparison**	**p-value**
100%	10 (13.2%)	1 (1.3%)	3 (3.9%)	3 (4.0%)	TRI vs. FH	0.005
90%	23 (30.3%)	6 (7.9%)	5 (6.6%)	9 (12.0%)	TRI vs. FR	0.042
75%	14 (18.4%)	15 (19.7%)	10 (13.2%)	9 (12.0%)	TRI vs. HR	0.045
50%	11 (14.5%)	12 (15.8%)	13 (17.1%)	17 (22.7%)		
25%	14 (18.4%)	29 (38.2%)	24 (31.6%)	25 (33.3%)		
No change	0	7 (9.2%)	16 (21.1%)	9 (12.0%)		
Worse	0	0	2 (2.6%)	0		
Missing	4 (5.3%)	6 (7.9%)	3 (3.9%)	3 (4.0%)		

Source: Summary is based on Sponsor's NDA submission (page 8-0045, Volume 31 and page 8-2081, Volume 37).
[1] Dichotomization analysis is reviewer's analysis and is based on Cochran-Mantel-Haenszel test adjusting for study site.

Table 5: Patient's Static Global Assessment at Day 56: ITT Analysis

	STUDY 28A				[1] Dichotomization analysis	
Global Assess.	**TRI (n=85)**	**FH (n=85)**	**FR (n=85)**	**HR (n=83)**	**Comparison**	**p-value**
Completely cleared	12 (14.1%)	2 (2.4%)	1 (1.2%)	6 (7.2%)	TRI vs. FH	0.002
Nearly cleared	51 (60.0%)	30 (35.3%)	16 (18.8%)	46 (55.4%)	TRI vs. FR	< 0.001
Significant hyperpigmentation	18 (21.2%)	49 (57.6%)	62 (72.9%)	26 (31.3%)	TRI vs. HR	0.071
Missing	4 (4.7%)	4 (4.7%)	6 (7.1%)	5 (6.0%)		
	STUDY 28B				[1] **Dichotomization analysis**	
Global Assess.	**TRI (n=76)**	**FH (n=76)**	**FR (n=76)**	**HR (n=75)**	**Comparison**	**p-value**
Completely cleared	6 (7.9%)	1 (1.3%)	1 (1.3%)	3 (4.0%)	TRI vs. FH	0.053
Nearly cleared	49 (64.5%)	28 (36.8%)	19 (25.0%)	25 (33.3%)	TRI vs. FR	0.053
Significant hyperpigmentation	17 (22.4%)	41 (53.9%)	52 (68.4%)	44 (58.7%)	TRI vs. HR	0.301
Missing	4 (5.3%)	6 (7.9%)	4 (5.3%)	3 (4.0%)		

Source: Summary is based on Sponsor's NDA submission (page 8-0046, Volume 31 and page 8-2082, Volume 37).
[1] Dichotomization analysis is reviewer's analysis and is based on Cochran-Mantel-Haenszel test adjusting for study site.

Table 6: Physician's Static Global Assessment at Day 56: ITT Analysis

	STUDY 28A				[1] Dichotomization analysis	
Global Assess.	**TRI (n=85)**	**FH (n=85)**	**FR (n=85)**	**HR (n=83)**	**Comparison**	**p-value**
Completely cleared	22 (25.9%)	2 (2.4%)	0	10 (12.0%)	TRI vs. FH	< 0.001
Nearly cleared	46 (54.1%)	30 (35.3%)	17 (20.0%)	37 (44.6%)	TRI vs. FR	< 0.001
Significant hyperpigmentation	13 (15.3%)	49 (57.6%)	63 (74.1%)	31 (37.3%)	TRI vs. HR	0.009
Missing	4 (4.7%)	4 (4.7%)	5 (5.9%)	5 (6.0%)		
	STUDY 28B				[1] **Dichotomization analysis**	
Global Assess.	**TRI (n=76)**	**FH (n=76)**	**FR (n=76)**	**HR (n=75)**	**Comparison**	**p-value**
Completely cleared	11 (14.5%)	1 (1.3%)	3 (3.9%)	3 (4.0%)	TRI vs. FH	0.003
Nearly cleared	39 (51.3%)	22 (28.9%)	16 (21.1%)	19 (25.3%)	TRI vs. FR	0.025
Significant hyperpigmentation	22 (28.9%)	47 (61.8%)	54 (71.1%)	50 (66.7%)	TRI vs. HR	0.027
Missing	4 (5.3%)	6 (7.9%)	3 (3.9%)	3 (4.0%)		

Source: Summary is based on Sponsor's NDA submission (page 8-0046, Volume 31 and page 8-2082, Volume 37).
[1] Dichotomization analysis is reviewer's analysis and is based on Cochran-Mantel-Haenszel test adjusting for study site.

For robustness of the efficacy results, this reviewer performed the analyses based on the last observation carried forward (LOCF) method for handling missing data. Results of the analyses were consistent.

4. Discontinuation and Missing Values

For each pivotal study (28A and 28B), the discontinuation rate ranged between 4.0% and 8.4% over treatment groups (see Table 1). The treatment arms were comparable within each study in terms of study completion rate.

Sponsor's analysis treated missing data as failures. This reviewer has performed ITT analysis based on the last observation carried forward (LOCF) method for missing values; the results were consistent as expected. Therefore, the impact of the discontinuation and missing values was minimal and did not affect the overall conclusion.

5. Subgroup Analyses

Subgroup efficacy results by race suggest that the treatment effect of Tri-Luma was generally similar across subgroups. No significant and clinically meaningful disparity conclusion among subgroups could be drawn.

It should be noted that more than 97% of enrolled subjects are female within each study. The subgroup efficacy results for female group are similar to those of the overall analysis as expected. However, the efficacy trend for male group cannot be drawn due to small sizes.

Results for the primary efficacy endpoint by study site are summarized in Table AII.5 of the Appendix. It can be observed that Tri-Luma treatment is numerically more effective than other dyad groups, except sites 4 and 6 in study 28B, where Tri-Luma had same success rate and no success as compared to HR group, respectively.

6. Concomitant Drug Use

Note that Sponsor's PP analyses (i.e. PP analyses in the submission and PP re-analysis dated 9/19/01) included subjects who used medication that should be excluded, as per the protocol. Each study had 45[3] such patients. Details on concomitant drug used by these subjects are listed on pages 8-0638 – 0640, Volume 33 and pages 8-2772 – 2775, Volume 40 of the Sponsor's NDA submission (dated 7/20/01).

The Sponsor indicated that such protocol deviation was considered to be minor because in all cases use of the excluded medication did not significantly affect the evaluation of efficacy or safety of the study drugs. The impact of these subjects on the efficacy results is studied.

Table AII.6 of the Appendix presents the number of subjects who used excluded medication by treatment groups for each study. No significant difference among groups is indicated. Table AII.7 of the Appendix presents results for the primary efficacy endpoint based on the PP population excluding these subjects:

- The conclusion is consistent with Sponsor's PP as well as ITT analyses for study 28A.
- For study 28B, Tri-Luma did not demonstrate superiority over dyads (p-value = 0.214 and 0.191 as compared to FR and HR group, respectively). The reasons are:
    - The success rate in TRI group was relatively small in study 28B.
    - Comparing the results in Table AII.7 with Table 2, the success count in the primary efficacy endpoint was the same for the dyad groups (i.e. FH, FR and HR groups), but the success count in TRI group was reduced by 3.

After consultation with the medical reviewer, the use of nasal/inhaled corticosteroid concomitant medication is not expected to have an effect on pigmentation. Therefore, a request was made that the Sponsor submitted an ITT analysis with exclusion of subjects who used non-nasal/inhaled corticosteroid concomitant medication. Results (pages 5-040, 5-049, 5-052, 5-058, 5-067 and 5-070 dated 11/22/01) were consistent to those in Table AII.7 of the Appendix.

In summary, the subjects who took excluded concomitant medication did contribute efficacy for Tri-Luma treatment in study 28B. The non-superiority of Tri-Luma to dyads in the primary efficacy endpoint based on the above analyses could also be due to the fact that sample sizes were reduced and, consequently, was not powered enough to detect the difference between treatments, in addition to a smaller success rate in TRI group. The medical reviewer should comment on whether such protocol deviation is minor and, consequently, did not significantly affect the evaluation of efficacy or safety of the study drugs. On the other hand, the Sponsor should perform additional analyses to address the issue that no bias involves in the efficacy results due to the concomitant drug usage.

III. Safety Review

Safety assessment of Tri-Luma and three dyads based on

(a) extent of exposure to the test medication; and

[3] Sponsor indicated that 36 subjects used concomitant drug that was excluded, as per the protocol in study 28B (page 8-2072, Volume 37). However, the listing on page 8-2772, Volume 40, consisted of 45 subjects.

(b) incidence rates of adverse events, serious adverse events and withdrawals due to adverse events

is summarized in Tables 7 and 8, respectively. The results presented in Tables 8(a) and 8(b) are based on studies 28A and 28B combined.

Table 7: Extent of Exposure to Study Medication

Duration of Exposure					
Study 28A	**TRI (n=85)**	**FH (n=85)**	**FR (n=85)**	**HR (n=83)**	**p-value**
Mean (s.d.)	56.9 (4.5)	55.9 (5.5)	55.9 (5.0)	56.2 (6.7)	0.634
Median	56.0	56.0	56.0	56.0	
Range (min, max)					
Study 28B	**TRI (n=76)**	**FH (n=76)**	**FR (n=76)**	**HR (n=75)**	**p-value**
Mean (s.d.)	56.4 (3.6)	55.8 (3.4)	56.1 (8.4)	56.6 (2.7)	0.799
Median	56.0	56.0	56.0	56.0	
Range (min, max)					

Average Daily Usage (in gram) of Study Medication (studies 28A and 28B combined)				
Statistic	**TRI (n=161)**	**FH (n=161)**	**FR (n=161)**	**HR (n=158)**
Mean (s.d.)	0.305 (0.235)	0.376 (0.275)	0.317 (0.263)	0.337 (0.256)
Median	0.242	0.297	0.244	0.262
Range (min, max)				

Source: Sponsor's NDA submission (pages 8-0049, Volume 31; 8-2085, Volume 37; and 8-3415, Volume 41)

Table 8(a): Overall Incidence of Adverse Events

Events	Tri-Luma (n=161)	FH (n=161)	FR (n=161)	HR (n=158)
Subjects with at least one adverse event	121 (75.2%)	95 (59.0%)	131 (81.4%)	138 (87.3%)
Total adverse events	385	192	354	426
Adverse events by intensity:				
Mild: total events	301	141	290	343
Moderate: total events	73	48	58	71
Severe: total events	11	3	5	11
Life Threatening: total events	0	0	0	1
Fatal: total events	0	0	1	0
Subjects with at least one **treatment-related** adverse event	102 (63.4%)	56 (34.8%)	105 (65.2%)	126 (79.7%)
Total **treatment-related** AEs	254	77	226	330
Adverse events by intensity:				
Mild: total events	222	66	205	280
Moderate: total events	28	11	19	44
Severe: total events	4	0	2	6
Life Threatening: total events	0	0	0	0
Fatal: total events	0	0	0	0
Subjects with adverse events resulting in discontinuation	0	1 (0.6%)	4 (2.5%)	1 (0.6%)
Serious adverse events	0	0	3 (1.9%)	1 (0.6%)
Deaths	0	0	1 (0.6%)	0

Source: Sponsor's NDA submission (page 8-3418, Volume 41; pages 8-3505, 8-3506, 8-3545, Volume 42).

Table 8(b): Summary of Most Common[1] Adverse Events

	Tri-Luma (n=161)	FH (n=161)	FR (n=161)	HR (n=158)
Subjects with at least one adverse event	121 (75.2%)	95 (59.0%)	131 (81.4%)	138 (87.3%)
Subjects with most common adverse events				
Desquamation	61 (37.9%)	6 (3.7%)	40 (24.8%)	97 (61.4%)
Erythema	66 (41.0%)	26 (16.1%)	41 (25.5%)	69 (43.7%)
Burning	29 (18.0%)	5 (3.1%)	33 (20.5%)	36 (22.8%)
Dryness	23 (14.3%)	5 (3.1%)	23 (14.3%)	21 (13.3%)
Pruritus	18 (11.2%)	5 (3.1%)	12 (7.5%)	34 (21.5%)
Headache NOS	16 (9.9%)	17 (10.6%)	13 (8.1%)	13 (8.2%)

Source: Sponsor's NDA submission (page 8-3419, Volume 41).
[1] Events occurred in at least 10% of patients in at least one treatment group.

The results in Tables 7 and 8 are summarized below:

- The duration of study drug exposure was comparable among treatment groups in each study (Table 7). The average daily drug usage in Tri-Luma group (0.305 gram) was generally comparable to others despite FH group (0.376 gram) may had a higher average daily usage.
- The majority of treatment-related adverse events were judged as mild. The incidence rate was generally comparable across treatment arms, but FH group had a lower rate (Table 8(a)).
- No subject in Tri-Luma group was discontinued due to adverse events; neither serious adverse event nor death was reported. One death was reported in FR group. According to the Sponsor, the subject died due to overdose of non-study medication, and consequently, was not related to the study drug (Table 8(a)).
- The most common adverse events in Tri-Luma group were desquamation and erythema (i.e. 37.9% and 41.0%, respectively). The erythema rate was similar to that in HR group (41.0% vs. 43.7%) and higher than FH and FR groups (41.0% vs. 16.1% and 25.5%). The desquamation rate in Tri-Luma arm was significantly lower than HR group (37.9% vs. 61.4%), but higher than FH and FR groups (37.9% vs. 3.7% and 24.8% in Table 8(b)).

IV. Summary and Conclusion

The Sponsor in this submission presented results for two pivotal studies (studies 28A and 28B) in support of the efficacy and safety claim of TRI-LUMA Cream for the treatment of melasma of the face. The cream was administered once daily before bedtime for 8 weeks in these trials.

Efficacy:

- Efficacy results from two pivotal trials based on the ITT population, treating missing data at Day 56 as failures, showed that Tri-Luma was superior to each of the three dyads in the primary efficacy endpoint, i.e. the proportion of subjects with investigator's assessment of melasma severity score of 0 at Day 56.

  For the secondary efficacy endpoints, Tri-Luma demonstrated superiority over dyads in:
  - Proportion of subjects with investigator's melasma severity score of 0 or 1 at Day 56.
  - Proportion of subjects with Physician's global improvement of 100% from baseline to Day 56.

- Proportion of subjects with Physician's Static Global assessment rated as "completely cleared" at Day 56.

It should be noted that Tri-Luma Cream did ***not*** demonstrate superiority over all dyads in the dichotomized Patient's Static Global assessment at Day 56 (i.e. the proportion of subjects with Patient's Static Global assessment rated as "completely cleared"). In the NDA submission, the Sponsor used rank analysis of variance to analyze patient's static global assessment. However, the Agency had recommended analyses of dichotomized patient's static global assessment rather than rank analysis of variance at the IND protocol review stage.

The efficacy results are summarized in the table below:

STUDY 28A		**TRI (n=85)**	**FH (n=85)**	**FR (n=85)**	**HR (n=83)**
Primary	Proportion of subjects with severity score of 0	32 (37.6%)	3 (3.5%)	0	12 (14.5%)
	Comparison, p-value	NA	< 0.001	< 0.001	< 0.001
Secondary	Proportion of subjects with severity score of 0 or 1	73 (85.9%)	42 (49.4%)	23 (27.1%)	51 (61.4%)
	Comparison, p-value	NA	< 0.001	< 0.001	< 0.001
	Proportion of subjects with phys's 100% global improvement	22 (25.9%)	2 (2.4%)	0	11 (13.3%)
	Comparison, p-value*	NA	< 0.001	< 0.001	0.020
	Proportion of subjects with patient's static global "completely cleared"	12 (14.1%)	2 (2.4%)	1 (1.2%)	6 (7.2%)
	Comparison, p-value*	NA	0.002	< 0.001	**0.071**
	Proportion of subjects with phys's static global rated as "completely cleared"	22 (25.9%)	2 (2.4%)	0	10 (12.0%)
	Comparison, p-value*	NA	< 0.001	< 0.001	0.009
STUDY 28B		**TRI (n=76)**	**FH (n=76)**	**FR (n=76)**	**HR (n=75)**
Primary	Proportion of subjects with severity score of 0	10 (13.2%)	1 (1.3%)	3 (3.9%)	3 (4.0%)
	Comparison, p-value	NA	0.005	0.042	0.045
Secondary	Proportion of subjects with severity score of 0 or 1	51 (67.1%)	26 (34.2%)	21 (27.6%)	23 (30.7%)
	Comparison, p-value	NA	< 0.001	< 0.001	< 0.001
	Proportion of subjects with phys's 100% global improvement	10 (13.2%)	1 (1.3%)	3 (3.9%)	3 (4.0%)
	Comparison, p-value*	NA	0.005	0.042	0.045
	Proportion of subjects with patient's static global "completely cleared"	6 (7.9%)	1 (1.3%)	1 (1.3%)	3 (4.0%)
	Comparison, p-value*	NA	0.053	0.053	**0.301**
	Proportion of subjects with phys's static global rated as "completely cleared"	11 (14.5%)	1 (1.3%)	3 (3.9%)	3 (4.0%)
	Comparison, p-value*	NA	0.003	0.025	0.027

Three primary comparisons are TRI vs. FH, TRI vs. FR, and TRI vs. HR.
* Dichotomized analysis is reviewer's analysis, which is based on Cochran-Mantel-Haenszel test adjusting for site.

Having said that two studies win on the primary efficacy endpoint, this reviewer, however, has the following concern about their randomization conduct:

Randomization: The issue of any selection bias in the efficacy results due to the way of assigning study sites to studies 28A and 28B as well as deviation from pre-planned randomization during the course of the trials is not addressed based on the Sponsor's submission. The Sponsor's assignment of site numbers in each study was not sequential. It is not clear whether such

assignment was a post-hoc and if so, its implication on the efficacy results. The Sponsor should provide clarification/justification to address this issue.

- Forty-five subjects (15%. See pages 8-2772 – 2775, Volume 40 of the NDA submission) in study 28B used concomitant drug. The Subjects who took excluded concomitant medication did contribute efficacy for Tri-Luma treatment in study 28B. The non-significant results between Tri-Luma and some dyads in the primary efficacy endpoint based on analysis excluding these subjects could be due to the fact that reduced sample sizes are not powered enough to detect the difference between treatments. The medical reviewer should comment on whether such protocol deviation is minor and, consequently, did not significantly affect the evaluation of efficacy or safety of the study drugs. On the other hand, the Sponsor should perform additional analysis to address the issue that no bias involves in the efficacy results due to the concomitant drug usage.

- It should be noted that more than 97% of enrolled subjects in studies 28A and 28B are females. Whether female subjects are the primary treated population for melasma indication is a clinical issue and should be commented by the clinical reviewer. Such information should be reflected on the labeling.

Safety:
Safety assessment for studies 28A and 28B based on the extent of exposure to the study drug as well as the incidence of adverse events are:

- The duration of study drug exposure was comparable among treatment groups. The average daily drug usage in Tri-Luma group (0.305 gram) was generally comparable to others despite FH group (0.376 gram) had a higher average daily usage.
- The majority of treatment-related adverse events were judged as mild. The incidence rate was generally comparable across treatment arms (TRI: FR: HR = 63.4%: 65.2%: 79.7%), but FH group (34.8%) had a significantly lower rate.
- No subject in Tri-Luma group was discontinued due to adverse events; neither serious adverse event nor death was reported. One death was reported in FR group. According to the Sponsor, the subject died due to overdose of non-study medication, and consequently, was judged not relate to the study drug.
- The most common adverse events in Tri-Luma group were desquamation and erythema (i.e. 37.9% and 41.0%, respectively). The erythema rate was similar to that in HR group (41.0% vs. 43.7%) and higher than FH and FR groups (41.0% vs. 16.1% and 25.5%). The desquamation rate in Tri-Luma arm was lower than HR group (37.9% vs. 61.4%), but higher than FH and FR groups (37.9% vs. 3.7% and 24.8%).

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Archival: NDA 21-112/N-000
HFD-540/Div. File
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HFD-725/Dr. Alosh
HFD-725/Dr. Lee

This review contains 29 pages (1 cover page, 1 page of table of contents, 2 pages of executive summary, 15 pages of text and 10 pages of Appendix)

APPENDIX A

Table AII.1: Patient Enrollment by Study Site

Study	Site ID	Investigator (Location)	Number of enrollment
28A	01	Dr. Torok (Medina, Ohio)	60
	03	Dr. Baumann (Miami, Florida)	74
	05	Dr. Wieder (LA, California)	25
	07	Dr. Jarratt (Austin, Texas)	58
	09	Dr. Pariser (Norfolk, Virginia)	33
	11	Dr. Martin (San Diego, California)	56
	13	Dr. Weiss/Shavin (Snellville, Georgia)	32
28B	02	Dr. Taylor (New York)	59
	04	Dr. Jones (Bryan, Texas)	44
	06	Dr. Lowe (Santa Monica, California)	40
	08	Dr. Rich (Portland, Oregon)	60
	10	Dr. Tschen (Albuquerque, New Mexico)	60
	12	Dr. Menter (Dallas, Texas)	40
Source: Sponsor's NDA submission (page 8-0018, Volume 31; page 8-2054, Volume 37; and Section 15.1.5, Volume 32).			

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Table AII.2: Patient Demographics and Baseline Characteristics: Studies 28A and 28B –ITT Population

STUDY 28A	Tri-Luma (n=85)	FH (n=85)	FR (n=85)	HR (n=83)	p-value
Age (years)					
Mean (s.d.)	41.4 (8.6)	42.7 (8.1)	41.3 (8.7)	40.7 (8.0)	0.464
Range	23.0 – 60.0	26.0 – 66.0	25.0 – 66.0	26.0 – 66.0	
Gender, n (%)					
Male	3 (3.5%)	1 (1.2%)	1 (1.2%)	1 (1.2%)	0.606
Female	82 (96.5%)	84 (98.8%)	84 (98.8%)	82 (98.8%)	
Race, n (%)					
White	56 (65.9%)	57 (67.1%)	64 (75.3%)	58 (69.9%)	0.175
Black	0	3 (3.5%)	2 (2.4%)	0	
Asian	4 (4.7%)	3 (3.5%)	2 (2.4%)	0	
Other	25 (29.4%)	22 (25.9%)	17 (20.0%)	25 (30.1%)	
Skin Prototype, n (%)					
Type I	8 (9.4%)	8 (9.4%)	8 (9.4%)	8 (9.6%)	0.946
Type II	27 (31.8%)	24 (28.2%)	31 (36.5%)	31 (37.3%)	
Type III	35 (41.2%)	40 (47.1%)	32 (37.6%)	33 (39.8%)	
Type IV	15 (17.6%)	13 (15.3%)	14 (16.5%)	11 (13.3%)	
Melasma severity, n (%)					
Moderate	69 (81.2%)	56 (65.9%)	63 (74.1%)	51 (61.4%)	[1] 0.015
Severe	16 (18.8%)	29 (34.1%)	22 (25.9%)	32 (38.6%)	
STUDY 28B	**Tri-Luma (n=76)**	**FH (n=76)**	**FR (n=76)**	**HR (n=75)**	**p-value**
Age (years)					
Mean (s.d.)	43.2 (9.4)	44.1 (10.6)	42.6 (9.4)	45.4 (8.8)	0.287
Range	22.0 – 66.0	21.0 – 75.0	22.0 – 74.0	30.0 – 71.0	
Gender, n (%)					
Male	1 (1.3%)	4 (5.3%)	1 (1.3%)	2 (2.7%)	0.378
Female	75 (98.7%)	72 (94.7%)	75 (98.7%)	73 (97.3%)	
Race, n (%)					
White	47 (61.8%)	51 (67.1%)	46 (60.5%)	43 (57.3%)	0.904
Black	4 (5.3%)	3 (3.9%)	5 (6.6%)	4 (5.3%)	
Asian	5 (6.6%)	5 (6.6%)	4 (5.3%)	8 (10.7%)	
Other	20 (26.3%)	17 (22.4%)	21 (27.6%)	20 (26.7%)	
Skin Prototype, n (%)					
Type I	6 (7.9%)	6 (7.9%)	7 (9.2%)	7 (9.3%)	0.649
Type II	21 (27.6%)	26 (34.2%)	19 (25.0%)	18 (24.0%)	
Type III	32 (42.1%)	22 (28.9%)	24 (31.6%)	24 (32.0%)	
Type IV	17 (22.4%)	22 (28.9%)	26 (34.2%)	26 (34.7%)	
Melasma severity, n (%)					
Moderate	55 (72.4%)	52 (68.4%)	48 (63.2%)	45 (60.0%)	[1] 0.330
Severe	21 (27.6%)	24 (31.6%)	28 (36.8%)	30 (40.0%)	

Source: Sponsor's NDA submission (pages 8-0037 and 8-0043, Volume 31; pages 8-2073 and 8-2079, Volume 37)
[1] Reviewer's analysis based on Cochran-Mantel-Haenszel test adjusting for study site.

Table AII.3: Investigator's Assessment of Melasma Severity at Day 56 by Baseline Disease Status – ITT Population

	STUDY 28A				
Treatment	**Baseline**	**Cleared (score =0)**	**Mild (score = 1)**	**Moderate (score=2)**	**Severe (score=3)**
Tri-Luma (n=85)	Moderate (n=69) Severe (n=16)	27 (31.8%) 5 (5.9%)	33 (38.8%) 8 (9.4%)	5 (5.9%) 3 (3.5%)	0 0
FH (n=85)	Moderate (n=56) Severe (n=29)	3 (3.5%) 0	31 (36.5%) 8 (9.4%)	20 (23.5%) 11 (12.9%)	0 9 (10.6%)
FR (n=85)	Moderate (n=63) Severe (n=22)	0 0	21 (24.7%) 2 (2.4%)	39 (45.9%) 7 (8.2%)	0 11 (12.9%)
HR (n=83)	Moderate (n=51) Severe (n=32)	10 (12.0%) 2 (2.4%)	25 (30.1%) 14 (16.9%)	13 (15.7%) 12 (14.5%)	1 (1.2%) 3 (3.6%)
	STUDY 28B				
Treatment	**Baseline**	**Cleared (score =0)**	**Mild (score = 1)**	**Moderate (score=2)**	**Severe (score=3)**
Tri-Luma (n=76)	Moderate (n=55) Severe (n=21)	9 (11.8%) 1 (1.3%)	30 (39.5%) 11 (14.5%)	13 (17.1%) 6 (7.9%)	0 2 (2.6%)
FH (n=76)	Moderate (n=52) Severe (n=24)	1 (1.3%) 0	20 (26.3%) 5 (6.6%)	28 (36.8%) 8 (10.5%)	0 8 (10.5%)
FR (n=76)	Moderate (n=48) Severe (n=28)	3 (3.9%) 0	14 (18.4%) 4 (5.3%)	28 (36.8%) 9 (11.8%)	0 15 (19.7%)
HR (n=75)	Moderate (n=45) Severe (n=30)	2 (2.7%) 1 (1.3%)	16 (21.3%) 4 (5.3%)	24 (32.0%) 10 (13.3%)	0 15 (20.0%)
Source: Sponsor's NDA submission (page 8-0043, Volume 31 and page 8-2079, Volume 37)					

Table AII.4: Proportion of Subjects with Severity Score of 0 at Day 56 – ITT Analysis (Reviewer's Sensitivity Analysis)

Table AII.4 (a)

	TRI (n=90)	FH (n=91)	FR (n=91)	HR (n=88)
Study 1 = {sites of 1, 2, 3, 4, 5, 6, 7}	27 (30.0%)	3 (3.3%)	2 (2.2%)	14 (15.9%)
p-value	N/A	< 0.001	< 0.001	0.015
	TRI (n=71)	**FH (n=70)**	**FR (n=70)**	**HR (n=70)**
Study 2 = {sites of 8, 9, 10, 11, 12, 13}	15 (21.1%)	1 (1.4%)	1 (1.4%)	1 (1.4%)
p-value	N/A	< 0.001	< 0.001	< 0.001
p-value is based on the Cochran-Mantel-Haenszel test adjusting for study site.				

Table AII.4 (b)

Study sites inclusion	TRI (n=97)	FH (n=97)	FR (n=96)	HR (n=95)
Study 1 = {sites of 1, 3, 4, 7, 9, 10, 11}	37 (38.1%)	4 (4.1%)	2 (2.1%)	14 (14.7%)
p-value	N/A	< 0.001	< 0.001	< 0.001
	TRI (n=64)	**FH (n=64)**	**FR (n=65)**	**HR (n=63)**
Study 2 = {sites of 2, 5, 6, 8, 12, 13}	5 (7.8%)	0	1 (1.5%)	1 (1.6%)
p-value	N/A	0.024	0.097	0.106
p-value is based on Cochran-Mantel-Haenszel test adjusting for study site.				

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Table AII.5: Proportion of Subjects with Severity Score of 0 at Day 56 by Study Site ITT Analysis – Studies 28A and 28B

Study 28A, c/n (%)					
Study site	**Total**	**TRI**	**FH**	**FR**	**HR**
1	60	9/15 (60%)	1/15 (6.7%)	0	8/15 (53.3%)
3	74	8/19 (42.1%)	0	0	2/18 (11.1%)
5	25	0	0	0	0
7	58	6/14 (42.9%)	1/15 (6.7%)	0	1/14 (7.1%)
9	33	5/9 (55.6%)	1/8 (12.5%)	0	1/8 (12.5%)
11	56	3/14 (21.4%)	0	0	0
13	32	1/8 (12.5%)	0	0	0
Study 28B, c/n (%)					
Study site	**Total**	**TRI**	**FH**	**FR**	**HR**
2	59	2/15 (13.3%)	0	1/15 (6.7%)	0
4	44	2/11 (18.2%)	1/11 (9.1%)	1/11 (9.1%)	2/11 (18.2%)
6	40	0	0	0	1/10 (10.0%)
8	60	1/15 (6.7%)	0	0	0
10	60	4/15 (26.7%)	0	1/15 (6.7%)	0
12	40	1/10 (10.0%)	0	0	0

Source: Sponsor's electronic submission (file names: H28A.xpt and H28B.xpt)

Table AII.6: Subjects Who Took Concomitant Medication

	TRI (n=85)	FH (n=85)	FR (n=85)	HR (n=83)	Total (n=338)
Study 28A	14 (16.5%)	14 (16.5%)	8 (9.4%)	9 (10.8%)	45 (13.3%)
	TRI (n=76)	**FH (n=76)**	**FR (n=76)**	**HR (n=75)**	**Total (n=303)**
Study 28B	10 (13.2%)	9 (11.8%)	15 (19.7%)	11 (14.7%)	45 (14.9%)

Table AII.7: Proportion of Subjects with Investigator's Melasma Severity Score of 0 – PP Analysis Excluding Subjects Who Took Concomitant Medication (Reviewer's Analysis)

STUDY 28A	**TRI (n=67)**	**FH (n=68)**	**FR (n=72)**	**HR (n=70)**
Proportion of subjects with severity score of 0	27 (40.3%)	2 (2.9%)	0	11 (15.7%)
Comparison	NA	< 0.001	< 0.001	< 0.001
STUDY 28B	**TRI (n=63)**	**FH (n=62)**	**FR (n=57)**	**HR (n=63)**
Proportion of subjects with severity score of 0	7 (11.1%)	1 (1.6%)	3 (5.3%)	3 (4.8%)
Comparison	NA	0.035	0.214	0.191

Source: Analysis is based on the Sponsor's electronic data set submission. Three comparisons are of interest: TRI vs. FH, TRI vs. FR, and TRI vs. HR. P-value for all comparisons is based on Cochran-Mantel-Haenszel test adjusting for study site.

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APPENDIX B

August 23, 2001

Dear Nini,

Here is the list of request for NDA 21,112 to facilitate stat. review:

- **Electronic SAS data sets (in transport file format) are needed for the review process.**
- **Request analyses on the primary and the secondary efficacy endpoints based on the Per-Protocol (PP) population originally defined in the protocol (i.e. all subjects who do not violate the protocol and complete 8-week of treatment).**
- **Request subgroup analysis by disease severity at baseline.**
- **Request detailed description of randomization for studies 28A and 28B.**

If you have any questions, please call me.

Vickey

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November 16, 2001

Request for Information on NDA 21-112 (Tri-Luma)

1. Randomization procedure (for studies 28A and 28B):
   - Please submit the randomization list for treatment allocation prior to initiation of the trials.
   - Please provide rationale and documentation of the study site inclusion for each study (i.e. study 28A included sites 1, 3, 5, 7, 9, 11, and 13; and study 28B included site 2, 4, 6, 8, 10, and 12).
   - Please provide details about the pre-planned randomization assignment to each study site (e.g. how many randomization numbers were assigned to each site). Please also provide any deviation from the pre-planned randomization, which occurred during the course of the trials, along with explanation of such deviation.

2. (Studies 28A and 28B) Please provide analyses for the primary and the secondary efficacy endpoints with exclusion of only the non-nasal/inhaled corticosteroid concomitant medications users.

3. (Studies 28A and 28B) Please submit ITT analyses for the primary and the secondary efficacy endpoints based on the last observation carried forward (LOCF) scheme for handling missing data.

APPENDIX C

Study 28A enrolled 338 subjects from sites 1, 3, 5, 7, 9, 11, and 13. Study 28B included sites 2, 4, 6, 8, 10 and 12, and enrolled 303 patients. The details of randomization assignment for each study site are summarized in the table below.

Randomization Assignment for Studies 28A and 28B

Study site	# of subjects	Randomization numbers assigned	First patient visit date	Last patient visit date
1	60	1 – 60	8/28/00	10/17/00
2	59	61 – 119	9/13/00	10/30/00
3	60	121 – 180	8/28/00	9/28/00
4	32	181 – 212	9/14/00	10/12/00
12	**12**	**213 – 224**	**9/29/00**	**10/31/00**
5	25	241 – 265	9/01/00	10/30/00
6	40	281 – 320	9/05/00	10/27/00
3	**14**	**321 – 334**	**9/28/00**	**10/31/00**
7	58	341 – 398	9/01/00	10/25/00
8	60	401 – 460	8/22/00	10/09/00
9	33	461 – 493	9/06/00	10/30/00
4	**12**	**509 – 520**	**10/12/00**	**10/31/00**
10	60	521 – 580	8/22/00	10/18/00
11	56	581 – 636	8/21/00	10/31/00
12	28	641 – 668	8/24/00	9/28/00
13	32	669 – 700	8/28/00	10/11/00
Total	**641**			

Source: Summary is based on the Sponsor's NDA submission (pages 8-0529 – 8-0545, Volume 32).

Reviewer's concerns about the Sponsor's randomization:

1. Study 28A included sites 1, 3, 5, 7, 9, 11 and 13; while study 28B included sites 2, 4, 6, 8, 10 and 12. The Sponsor's response (dated 11/22/01) indicated that "*the investigational sites chosen from Hill Dermaceuticals, Inc, [redacted] databases were randomly assigned site numbers from 1 to 13, the centers with odd numbers were assigned to conduct protocol 28A and the sites with the even numbers were assigned to conduct protocol 28B. Thus divided, centers were then checked for balanced geographic distribution*". However, it is not clear from the Sponsor's documentation whether the assignment of site numbers was a post-hoc or prior to initiation of the trials.

2. Neither documentation (at the IND protocol stage) regarding the number of randomization codes assigned to each study site prior to initiation of the trials, nor the deviation in assignment for some study sites (i.e. sites 3, 4, and 12) are provided. For instance (please also see the above table), site 3 in study 28A enrolled 74 subjects and patients' identification numbers were allocated with 121-180 and 321-334. In study 28B, site 4 enrolled 44 subjects; however, patients were allocated with numbers of 181-212 and 509-520. Similarly, site 12 enrolled 40 subjects with patient numbers of 213-224 and 641-668.

The Sponsor responded (dated 11/22/01, page 5-003) that each site was assigned a specified number of patients, 60 per site. However, during the course of the trials, some investigators indicated that enrollment of 60 patients cannot be met. These investigators were, therefore, given 40 pre-numbered treatment packs instead of 60. Also, note that the Sponsor indicated that pre-numbered treatment packets (according to the randomized code) sent to each investigator were shipped in increments of 20.

Based on the Sponsor's submission, the issue of any selection bias due to the way of assigning study sites to studies 28A and 28B as well as deviation from pre-planned randomization during the course of the trials is not addressed. The Sponsor should provide clarification/justification to address this issue.

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/s/

Showjien Lee
12/14/01 03:03:51 PM
BIOMETRICS

Mohamed Alosh
12/17/01 11:52:31 AM
BIOMETRICS
Concur with review

Mohammad Huque
1/15/02 11:34:06 AM
BIOMETRICS

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/s/

Showjien Lee
12/14/01 03:03:51 PM
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Concur with review

Mohammad Huque
1/15/02 11:34:06 AM
BIOMETRICS

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Addendum of Statistical Review

NDA #:	NDA 21-112
Applicant:	Hill Dermaceuticals, Inc.
Name of Drug:	Tri-Luma Cream
Route of Administration:	Topical
Indication:	Melasma of the face
Documents Reviewed:	Sponsor's responses dated 12/26/01, 12/27/01, 12/28/01, 01/04/02, 01/08/02 and 01/11/02
Related INDs:	[redacted]
Related NDAs:	NDA 21-112
Statistical Reviewer:	Shiowjen Lee, Ph.D. (HFD-725)
Medical Officer:	Hon-Sum Ko, M.D. (HFD-540)

I. Introduction:

The statistical review for NDA 21,112 raised issues about the assignment of sites to studies 28A and 28B as well as deviation from pre-planned randomization during the course of the trials based on the Sponsor's submissions dated 7/20/01, 9/19/01 and 11/22/01. The Sponsor's assignment of site numbers in each study was not sequential (i.e. odd number sites as one study and even number sites as another study). It is not clear whether such assignment was a post-hoc and if so, the implication on the efficacy results.

The Agency and Hill Dermaceuticals had a teleconference on 12/21/2001 to discuss further their randomization procedure. The Agency requested the Sponsor to provide an explanation, supported by documentation, of the randomization procedure and any deviation:

1. randomization generation program along with output
2. allocation of study sites to each study
3. deviation of assigning 60 numbers to each site
4. two sequences of randomization numbers for each of sites 4 and 12
5. deviation of some sites in the treatment packet shipment in increment of 20 to each site

For detailed discussion, please see Appendix A for the minutes of teleconference on 12/21/01. Sponsor's submissions (dated 12/26/01, 12/27/01 and 12/28/01) included responses to the clinical and statistical reviewers' requests. As clarification for some responses was needed, the Agency and the Sponsor had a follow-up teleconference on 01/04/02. The Agency requested the Sponsor to submit the following items, supported by documentation:

- randomization generation program along with output
- clarification of the number of study sites planned in studies 28A and 28B
- clarification of treatment-packet shipment in studies 28A/28B and verification of the number of treatment packets sent to study site 3 on 8/14/00 and 8/21/00.

Please see Appendix B for the minutes of teleconference on 01/04/02. Their responses were submitted on 01/04/02 via a fax and 01/08/02 via an e-mail. Another follow-up teleconference, which re-iterated the request of the original randomization program used along with output, was made on 01/09/02. The Sponsor's response was received via e-mail on 01/11/02.

II. Randomization Review:

According to the Sponsor (submission dated 12/26/01), the study sites were chosen prior to the start of the clinical trials. Ten sites with an allocation of 60 patients per site were planned initially. Seven hundred randomization codes were then prepared via a SAS program by ——. The randomization codes were sent to the Sponsor on 05/16/00 for conducting clinical trials (please see ' which was provided in the Sponsor's 12/27/01 responses to the clinical reviewer's requests).

It should be noted that the Sponsor did not submit the actual computer program, on floppy diskette, used for generation of the treatment allocation for studies 28A and 28B instead they provided a program code as a word document, where the document indicated the generation date of 04/13/00. This makes it difficult to verify the Sponsor's claim about the time and actual treatment allocation generated.

Having said that, this reviewer has the following comments about the submitted computer code as well as the output:

1. The computer program allowed for generation of 400 randomization codes instead of the claimed total of 700 randomization codes (see Appendix C).
2. The initial value (i.e. SEED) used for generating the 400 codes in (1) was given in the program, whereas the Sponsor's response indicated that the "SEED" for generating the additional 300 codes is not known at the time of the Sponsor's response (i.e. 01/11/02, see Appendix C). This makes it difficult to verify the treatment allocation for the 300 codes.
3. There are minor inconsistencies between the Sponsor's randomization codes submitted as an output on 01/11/02 and those in the submissions dated 07/20/01 and 12/26/01. However, change in the treatment codes for these patients does not affect the efficacy results.

According to the Sponsor, an internal meeting was held on 6/12/00 for discussion of the Tri-Luma development plan and a list of possible investigators (i.e. 14 selected sites and 4 in reserve) to participate in the studies. Thirteen investigators agreed to conduct the trials after the Sponsor contacted them. These study sites were then randomly assigned sequential numbers from 1 to 13. The Sponsor indicated that the assignment of odd numbered sites to study 28A and even numbered sites to study 28B was decided arbitrarily and was not recorded or documented. The assignment of patient numbers per site (i.e. 60 patients per site) was deviated due to the fact that only 700 codes were prepared for 13 study sites. The Sponsor's patient numbers allocation for each site is presented in Table 1.

Table 1. Patient Numbers Allocation

Site	# of patients	Patient numbers allocation	Site	# of patients	Patient numbers allocation
1	60	001-060	8	60	401-460
2	60	061-120	9	60	461-520
3	60	121-180	10	60	521-580
4	60	181-240	11	60	581-640
5	40	241-280	12	28	641-668
6	60	281-340	13	32	669-700
7	60	341-400			

Note that site 5 was allocated only 40 patients. According to the Sponsor, this was per the site investigator's (Dr. Wieder) request. The Sponsor indicated that the allocation of 28 and 32 patients for sites 12 and 13 was made to fit the pre-prepared 700 randomization codes. The decision to assign 28 patients to site 12 and 32 patients to site 13 was a random choice.

In explaining the shipment of drugs to the investigators, the Sponsor indicated (submission dated 12/26/01) that the shipment of the numbered treatment packets was such that each shipment included multiples of 4 rather than increment of 20 as described in the previous submission dated 11/22/01. The shipment based on increment of 20 was done for study 29, but not for studies 28A and 28B. The detailed shipment dates as well as the numbered treatment packets shipped to each site in studies 28A and 28B are shown in Appendix D.

The treatment-packet shipments in Appendix D show that:
(1) Each of the two treatment-packet shipments (shipped on 08/14/00 and 08/21/00) to site 3 was not multiples of 4 or 20, as 30 packets were shipped each.
(2) Sponsor made shipments to each site two or more times. There were three sites (i.e. sites 3, 4 and 12) with non-sequential patient numbered packet shipments.

The Agency asked the Sponsor to clarify whether there was an error in their shipment data (teleconference on 01/04/02) to site 3. The Sponsor responded (via fax on 01/04/02) that there was no error in the numbers of treatment packet sent to site 3. According to the Sponsor, this was due to an oversight that the 1st shipment sent to site 3 (dated 08/14/00) was not in multiples of 4, after the treatment packets were shipped out. Consequently, to avoid breaking the sequence of numbering and the multiples of 4 factor, the 2nd shipment of 30 packets was sent on 08/21/00 to complete the 60 allotted numbers for site 3.

The Sponsor's justification on multiples of 4 in the shipments to site 3 seems reasonable to this reviewer as the 1st patient enrollment date was 08/28/00 (see Sponsor's submission, page 8-0532, Volume 32), which was later than the two shipment dates, 08/14/00 and 08/21/00.

According to the Sponsor, multiple shipments were sent to study sites due to the following reasons:
a. To ensure that drugs were properly and securely stored, small quantities of the study drug were sent.
b. Due to the desire to enroll the maximum number of patients as soon as possible, constant monitoring enabled the Sponsor and the monitors to determine which sites were able to empanel more than 60 patients, and able to recruit more patients into the study. Upon request from the investigator and approval by the Sponsor, the numbered study drugs that had not been shipped to the assigned site were then re-assigned to the investigational site(s) that had recruited more patients.

Based on the reasons stated above and during the course of the trials, the Sponsor re-assigned treatment packet numbers 321-340 to site 3 from site 6, as site 3 had fast enrollment pace. Site 6 received only 40 treatment packets as per verbal request from the investigator. The numbered drugs assigned to site 4, 213 to 240 were re-assigned to site 12 due to a faster rate of enrollment at site 12. However, by the time site 4 requested more drug packets, only treatment packets

numbered 493 to 520 were remaining at Hill. According to the Sponsor, they decided to reserve packet numbered 493 to 508 for site 9 and re-assigned numbers 509 to 520 to site 4.

This reviewer examined the patient enrollment dates (submission dated 07/20/01) as well as the shipment information provided by the Sponsor (submission dated 12/26/01) and concluded that it is unlikely to have patient selection bias due to the non-sequential randomization numbers allocated. The reasons are:

- During the recruitment period between the end of August and the end of October 2000, site 3 had a fast pace of enrollment and completed the pre-assigned 60 patient numbers on 9/28/00. Site 6 was pre-assigned 60 patient numbers and the 1st patient was enrolled on 9/5/00. By the time of 9/25/00 [1] (i.e. the shipment date for both sites 3 and 6), only 28 subjects were enrolled in site 6. As per verbal request from the investigator of site 6, site 6 was allocated 40 numbers, 281-320. Consequently, it was reasonable to re-assign patient numbers 321-340 to site 3.
- The first patient enrolled in site 4 was on 9/14/00, which was relatively later than that for other sites even though the 1st treatment-packet shipment date was similar to others (8/16/00). Site 12 was pre-assigned 28 numbers and started the 1st enrollment on 8/24/00. Site 12 made the 2nd shipment request by the time of 9/14/00. Therefore, it was plausible to re-allocate 28 patient numbers (i.e. 213-240) from site 4 to site 12, as site 12 had about 1.5 months (till the end of October) to enroll more patients.
- As only 32 numbers remained in site 4, the enrollment was completed on 10/12/00. By the time of 10/3/00 (i.e. the 2nd shipment date for site 4), site 9 enrolled only 10 patients (i.e. patient numbers of 461 – 470) during the period of 9/6/00 – 10/3/00. This implied that site 9 had a slower enrollment rate as compared with other sites. Furthermore, only treatment packets numbered 493 to 520 were remaining at Hill. Consequently, it was reasonable to re-assign 12 patient numbers, 509-520, to site 4.

III. Site Allocation to Study

The Sponsor indicated that the allocation of sites to each study was done arbitrarily and was not pre-specified in the protocols. Per the medical team's request and following the discussion with the biostatistics team leader about carrying out an analysis to investigate the impact of study site allocation on the efficacy results, a sensitivity analysis is performed. The results of two scenarios are summarized in Tables 4 and 5, respectively. For the purpose of comparison, results of the original analysis as well as the response rates by study site are presented in Tables 2 and 3, respectively.

The analysis in Table 4 grouped the first seven site numbers 1-7 as one study, and other sites as another study. The conclusion is consistent with that in the original analysis (i.e. Tri-Luma is superior to all dyads in each of two studies). The analysis in Table 5, which is rather an extreme case, grouped study sites with the best 7 Tri-Luma response rates as one study, and other sites as another study. The results showed non-significance for the comparisons of TRI vs. FR and HR (p-value = 0.097 and 0.106) in the 2nd study group. But the results in the 1st study group are significant (p-value < 0.001).

[1] The use of shipment date is for discussion purpose. This may not be equivalent to, but should be close to, the shipment request date.

Table 2: Proportion of Subjects with Melasma Severity Score of 0 at Day 56 (Sponsor's Original Analysis)

SUTDY 28A	TRI (n=85)	FH (n=85)	FR (n=85)	HR (n=83)	Comparison	p-value
ITT analysis n (%)	32 (37.6%)	3 (3.5%)	0	12 (14.5%)	TRI vs. FH TRI vs. FR TRI vs. HR	< 0.001 < 0.001 < 0.001
STUDY 28B	**TRI (n=76)**	**FH (n=76)**	**FR (n=76)**	**HR (n=75)**	**Comparison**	**p-value**
ITT analysis n (%)	10 (13.2%)	1 (1.3%)	3 (3.9%)	3 (4.0%)	TRI vs. FH TRI vs. FR TRI vs. HR	0.005 0.042 0.045
Source: Sponsor's NDA submission (pages 8-0039 and 8-0096, Volume 31 and pages 8-2075 and 8-2126, Volume 37)						

Table 3: Proportion of Subjects with Melasma Severity Score of 0 at Day 56 by Study Site ITT Analysis – Studies 28A and 28B

Study 28A, c/n (%)					
Study site	**Total**	**TRI**	**FH**	**FR**	**HR**
1	60	9/15 (60%)	1/15 (6.7%)	0	8/15 (53.3%)
3	74	8/19 (42.1%)	0	0	2/18 (11.1%)
5	25	0	0	0	0
7	58	6/14 (42.9%)	1/15 (6.7%)	0	1/14 (7.1%)
9	33	5/9 (55.6%)	1/8 (12.5%)	0	1/8 (12.5%)
11	56	3/14 (21.4%)	0	0	0
13	32	1/8 (12.5%)	0	0	0
Study 28B, c/n (%)					
Study site	**Total**	**TRI**	**FH**	**FR**	**HR**
2	59	2/15 (13.3%)	0	1/15 (6.7%)	0
4	44	2/11 (18.2%)	1/11 (9.1%)	1/11 (9.1%)	2/11 (18.2%)
6	40	0	0	0	1/10 (10.0%)
8	60	1/15 (6.7%)	0	0	0
10	60	4/15 (26.7%)	0	1/15 (6.7%)	0
12	40	1/10 (10.0%)	0	0	0
Source: Sponsor's electronic submission (file names: H28A.xpt and H28B.xpt)					

Table 4: Proportion of Subjects with Melasma Severity Score of 0 at Day 56 – ITT Analysis (Reviewer's Sensitivity Analysis)

Study sites inclusion	**TRI (n=90)**	**FH (n=91)**	**FR (n=91)**	**HR (n=88)**
Study 1 = {sites of 1, 2, 3, 4, 5, 6, 7}	27 (30.0%)	3 (3.3%)	2 (2.2%)	14 (15.9%)
p-value	N/A	< 0.001	< 0.001	0.015
	TRI (n=71)	**FH (n=70)**	**FR (n=70)**	**HR (n=70)**
Study 2 = {sites of 8, 9, 10, 11, 12, 13}	15 (21.1%)	1 (1.4%)	1 (1.4%)	1 (1.4%)
p-value	N/A	< 0.001	< 0.001	< 0.001
p-value is based on the Cochran-Mantel-Haenszel test adjusting for study site.				

Table 5: Proportion of Subjects with Melasma Severity Score of 0 at Day 56 – ITT Analysis (Reviewer's Sensitivity Analysis)

Study sites inclusion	TRI (n=97)	FH (n=97)	FR (n=96)	HR (n=95)
Study 1 = {sites of 1, 3, 4, 7, 9, 10, 11}	37 (38.1%)	4 (4.1%)	2 (2.1%)	14 (14.7%)
p-value	N/A	< 0.001	< 0.001	< 0.001
	TRI (n=64)	**FH (n=64)**	**FR (n=65)**	**HR (n=63)**
Study 2 = {sites of 2, 5, 6, 8, 12, 13}	5 (7.8%)	0	1 (1.5%)	1 (1.6%)
p-value	N/A	0.024	0.097	0.106
p-value is based on Cochran-Mantel-Haenszel test adjusting for study site.				

IV. Summary and Conclusion:

Based on the Sponsor's submission (dated 12/26/01, 12/27/01, 12/28/01, 01/04/02, 01/08/02 and 01/11/02), the following are comments concerning the statistical items requested by the Agency at the teleconferences on 12/21/01, 01/04/02 and 01/09/02:

1. Original randomization generation program used along with output.
   Comment: The Sponsor indicated that the randomization codes were prepared on 04/13/00 by [redacted] The codes were sent to the Sponsor on 05/16/00 for conducting clinical trials (please see [redacted], which was provided in the Sponsor's 12/27/01 responses to the clinical reviewer's requests). However, it should be noted that the Sponsor did not submit the actual computer program, on floppy diskette, used for generation of the treatment allocation instead they provided a program code as a word document (dated 01/08/02). This makes it difficult to verify the Sponsor's claim about the time and actual treatment allocation generated.

   Having said that, this reviewer has the following comments about the submitted computer code as well as the output:
   (1) The computer program allowed for generation of 400 randomization codes instead of the claimed total of 700 randomization codes (see Appendix C).
   (2) The initial value (i.e. SEED) used for generating the 400 codes in (1) was given in the program, whereas the Sponsor's response indicates that the "SEED" for generating the additional 300 codes is not known at the time of the Sponsor's response (i.e. 01/11/02, see Appendix C). This makes it difficult to verify the treatment allocation for the 300 codes.
   (3) There are minor inconsistencies between the Sponsor's randomization codes submitted as an output on 01/11/02 and those in the submissions dated 07/20/01 and 12/26/01. However, change in the treatment codes for these patients does not affect the efficacy results.

2. Allocation of centers to each study and number of study sites planned.
   Comment: The Sponsor indicated that ten sites with an allocation of 60 patients per site were planned initially. Seven hundred randomization codes were then prepared via a computer

program. The Sponsor held an internal meeting on 6/12/00 to discuss the Tri-Luma development plan and list of possible investigators (i.e. 14 selected sites and 4 in reserve) to participate in the studies. Thirteen investigators agreed to conduct the trials after the Sponsor contacted them. These study sites were then randomly assigned sequential numbers from 1 to 13. However, the allocation of sites to each study (i.e. studies 28A and 28B) was arbitrary and was not pre-specified in the protocol.

3. Deviation of assigning 60 numbers to each site.
   Comment: The Sponsor indicated that some sites were allocated less than 60 patients each due to the fact that there were 700 randomization codes available for 13 study sites. The Sponsor's allocation of patients for each site prior to the conduct of the trials was included (see Table 1). Site 5 was allocated only 40 patients per the site investigator's request. The allocation of 28 and 32 patients for sites 12 and 13 was made to fit the pre-planned 700 randomization codes and the decision was a random choice. The explanation seems reasonable to this reviewer.

4. Two sequences of randomization numbers for each of sites 4 and 12.
   Comment: This reviewer examined the patient enrollment dates (submission dated 07/20/01) as well as the shipment information provided by the Sponsor (submission dated 12/26/01) and concluded that it is unlikely to have patient selection bias due to the non-sequential randomization numbers allocated. The reasons are:

- During the recruitment period between the end of August and the end of October 2000, site 3 had a fast pace of enrollment and completed the pre-assigned 60 patient numbers on 9/28/00. Site 6 was pre-assigned 60 patient numbers and the 1st patient was enrolled on 9/5/00. By the time of 9/25/00 (i.e. the shipment date for both sites 3 and 6), only 28 subjects were enrolled in site 6. As per verbal request from the investigator of site 6, site 6 was allocated 40 numbers, 281-320. Consequently, it was reasonable to re-assign patient numbers 321-340 to site 3.
- The first patient enrolled in site 4 was on 9/14/00, which was relatively later than that for other sites even though the treatment-packet shipment date was similar to others (8/16/00). Site 12 was pre-assigned 28 numbers and started the 1st enrollment on 8/24/00. Site 12 made the 2nd shipment request by the time of 9/14/00. Therefore, it was plausible to re-allocate 28 patient numbers (i.e. 213-240) from site 4 to site 12, as site 12 had about 1.5 months (till the end of October) to enroll more patients.
- As only 32 numbers remained in site 4, the enrollment was completed on 10/12/00. By the time of 10/3/00 (i.e. the 2nd shipment date for site 4), site 9 enrolled only 10 patients during the period of 9/6/00 – 10/3/00. This implied that site 9 had a slower enrollment rate as compared with other sites. Furthermore, only treatment packets numbered 493 to 520 were remaining at Hill. Consequently, it was reasonable to re-assign 12 patient numbers, 509-520, to site 4.

5. Deviation of some sites in the treatment packet shipment in increment of 20 to each site and verification of the number of treatment packets sent to study site 3 on 08/14/00 and 08/21/00.
   Comment: The Sponsor indicated (submission dated 12/26/01) that the shipment of the numbered treatment packets was such that each shipment included multiples of 4 rather than increment of 20 as described in the previous submission dated 11/22/01. The shipment based

on increment of 20 was done for study 29, but not for studies 28A and 28B. The treatment-packet shipments in Appendix D, however, show that:

- Each of the two treatment-packet shipments (shipped on 08/14/00 and 08/21/00) to site 3 was not multiples of 4 or 20, as 30 packets were shipped each.

According to the Sponsor, the deviation was due to an oversight that the 1st shipment sent to site 3 (dated 08/14/00) was not in multiples of 4, after the treatment packets were shipped out. Consequently, to avoid breaking the sequence of numbering and the multiples of 4 factor, the 2nd shipment of 30 packets was sent on 08/21/00 to complete the 60 allotted numbers for site 3.

The Sponsor's justification on multiples of 4 in the shipments to site 3 seems reasonable to this reviewer as the 1st patient enrollment date was 08/28/00 (see Sponsor's submission, page 8-0532, Volume 32), which was later than the two shipment dates, 08/14/00 and 08/21/00.

As the Sponsor's allocation of sites to each study (i.e. studies 28A and 28B) was arbitrary and was not pre-specified in the protocol, a sensitivity analysis about the site allocation to study was performed. The analysis showed that Tri-Luma cream is generally statistically superior to each of the three dyads. Tri-Luma is numerically better than each of the dyads even for the extreme scenario case.

Shiowjen Lee, Ph.D.
Mathematical Statistician, Biometrics III

Concur: Mohamed Alosh, Ph.D.
Team Leader, Biometrics III

Concur: Mohammad Huque, Ph.D.
Division Director, Biometrics III

cc:
Archival: NDA 21-112
HFD-540/Div. File
HFD-540/Dr. Wilkin
HFD-540/Dr. Ko
HFD-540/Ms. Lutwak
HFD-710/Dr. Anello
HFD-725/Dr. Huque
HFD-725/Dr. Alosh
HFD-725/Dr. Lee

APPEARS THIS WAY
ON ORIGINAL

This addendum contains 14 pages (8 pages of text and 6 pages of Appendix).

APPENDIX A

MEMORANDUM OF MEETING MINUTES

Date: December 21, 2001
NDA 21-112
Sponsor: Hill Dermaceuticals.
Type: teleconference
Purpose: A request for information

FDA Attendees:
Mohamed Alosh, Ph.D./Team Leader, Biostatistics DBIII, HFD-725
Shiowjen Lee, Ph.D., Reviewer, Biostatistics DBIII, HFD-725

Victoria Lutwak, Project Manager, HFD-540

Hill Attendees:
Rosario Ramirez, M.D.

Teleconference with Hill about Randomization Issue: (NDA 21,112 – TRI-LUMA Cream)

The Agency and Hill Dermaceuticals had a teleconference on 12/21/2001 concerning the Sponsor's randomization procedure. The teleconference was started by acknowledging receipt of the Sponsor's responses to a previous request concerning the randomization and indicated that additional material would be helpful for completing the review.

The Sponsor explained that the allocation of odd/even numbered sites to studies was done at random, but was not pre-specified in their protocol. Additionally, the Sponsor indicated that 700 patients were originally planned prior to the actual enrollment in the trials. Treatment allocation to these planned subjects was carried out using a computer program. Then following a discussion about the number of patients allocated to each site, the Sponsor indicated that they had planned 11 sites for the two studies, then 2 additional sites were added later. Consequently, these 2 sites were not allocated with 60 patients each. The Sponsor indicated that, during the course of the trials, some investigators would not be able to enroll 60 subjects and, consequently, some of the patient numbers were re-assigned to other sites.

Dr. Alosh requested that, to facilitate the review, the Sponsor should provide any documentation they have concerning the allocation of centers to each study, as even numbered sites were assigned to Study 28B and odd numbered sites were assigned to Study 28A. In addition, Dr. Alosh asked whether the treatment allocation codes were generated prior to start of the trials. He requested that the Sponsor submit randomization-generation program along with outputs for the Agency's review. The discussion then moved to the Sponsor's submission, which indicated that each site was assigned a specified number of randomization numbers, 60 per site. The Sponsor indicated that the

specification of 60 per site was decided prior to the trials. Furthermore, they indicated that, in principle, each site was assigned 60 numbers, but they had only generated 700 numbers. Therefore, only the 1st 11 sites were assigned with 60 numbers. Dr. Alosh asked the Sponsor to provide documentation concerning such deviation.

Dr. Lee requested the Sponsor to provide details about the patients enrollment in sites 4 and 12, as patients in each of these sites did not have sequential numbers (i.e. each site had two sequences of randomization numbers). In addition, the Sponsor indicated that the pre-number treatment packets were shipped in increments of 20 to each investigator site. However, the randomization number in site 12, for example, started at 213. Dr. Lee requested the Sponsor to provide documentation and clarification concerning such deviation.

In Summary, the Sponsor agreed to submit the following items for the Agency's review:

1. randomization generation program along with output
2. documentation concerning allocation of centers to each study
3. documentation concerning the deviation of assigning 60 numbers to each site
4. documentation and clarification concerning two sequences of randomization numbers for each of sites 4 and 12
5. documentation and clarification concerning the deviation of some sites in the treatment packet shipment in increment of 20 to each site

APPENDIX B

MEMORANDUM OF TELEPHONE CONVERSATION

Meeting Minutes
Date: January 4, 2002
Type: T-con
NDA 21-112 TRI-LUMA (fluocinolone acetonide/hydrocortisone/tretinoin) Cream
Sponsor: Hill Dermaceuticals, Inc.

Attendees:
FDA: Shiowjen Lee, Ph.D., E. Pappas, and V. Lutwak
Hill Dermaceuticals: Nini Ramirez, Nancy Puglia, Jerry Roth

Telephone number: 1-800-344-5707

Background:
Submission dated July, 20, 2001; rec'd July 25, 2001.
Response to NA Letter

Teleconference with Hill at 10:00am, 01/04/2002:

Biometrics

The Agency and Hill Dermaceuticals had a teleconference on 01/04/2002 to request for some clarification on the documents the Sponsor submitted on 12/26/01, 12/27/01 and 12/28/01.

Dr. Lee requested the randomization generation program along with output, supported by documentation, be provided, as such request was made in the teleconference with the Sponsor on 12/21/01, but the generation program was not included in the submissions.

Dr. Lee asked for an explanation of the discrepancy among documents the Sponsor submitted concerning the number of study sites pre-planned prior to start of the trials. That is, 10 study sites were on the document in response to the statistical reviewer's request (dated 12/26/01), 14 sites were on the document in response to the clinical reviewer's request (dated 12/27/01), and 11 sites were on the Agency's minutes of teleconference (dated 12/21/01). The Sponsor indicated that 10 sites with 60 patients/per site were planned the earliest. Consequently, 700 randomization codes were generated from computer. Then they had an internal meeting on 6/12/00 for discussion of the Tri-Luma development plan. They then noticed that more than 10 sites could be participated – 14 sites were selected, and 4 were in reserve. They then decided to keep the enrollment of 40-60 patients per site.

Dr. Lee asked for the clarification on whether the treatment-packet shipment was in the increment of 20, or in multiples of 4. The Sponsor indicated that shipment in increment of 20 was done in study 29, but not in studies 28A and 28B. The shipment in studies 28A

and 28B was in multiples of 4. Dr. Lee then asked the Sponsor that site 3 had 30 packets shipped out on 8/14/00 and 8/21/00, respectively, which was not in multiples of 4. The Sponsor replied that they would check the numbers of treatment packets shipped to study site 3.

In Summary, the Sponsor agreed to submit the following items, supported by documentation:

1. randomization generation program along with output
2. clarification of the number of study sites planned in studies 28A and 28B
3. clarification of treatment-packet shipment in studies 28A/28B and verification of the number of treatment packets sent to study site 3 on 8/14/00 and 8/21/00.

CMC:

1. The chemist requested that the sponsor send three copies of the Methods Validation Package to the NDA. We provided, via fax, information on the content and organization of the Methods Validation Package to assist the sponsor with the submission.

2. The reviewer requested that the sponsor revise the "Summary Table of Testing Methods" (4 0010) to include phase separation. We requested a fax copy of the revised table.

3. The last item was to have the sponsor confirm that the 5 gram tube was a physician sample. They did. We then inquired where the stability information on this size was located in the NDA and were properly informed.

APPENDIX C

-----Original Message-----
From: [redacted]
Sent: Friday, January 11, 2002 8:57 AM
To: Nini Ramirez, MD
Subject: SAS Program for randomization code

Hi, Nini:
Attached is the SAS program for developing the randomization code. The seed used for developing the first 400 codes is given in the program. The output for the first 400 codes is also attached, as a work file. I do not know what seed was used to generate the other 300 codes that you asked for later. I hope that this will take care of the Agency statistician's questions.
Sincerely,
Innes

APPEARS THIS WAY
ON ORIGINAL

APPENDIX D

Data on Drug Product Shipment

Site	Date shipped	Patient code #'s	# of packets shipped
1	08/16/00 09/11/00	001-032 033-060	
2	08/24/00 10/03/00	061-092 093-120	
3	08/14/00 08/21/00 09/25/00	121-150 151-180 **321-340**	
4	08/16/00 10/03/00	181-212 **509-520**	
5	08/16/00 09/25/00	241-260 261-280	
6	08/16/00 09/25/00	281-312 313-320	
7	08/16/00 09/18/00	341-372 373-400	
8	08/16/00 09/13/00	401-432 433-460	
9	08/16/00 10/16/00	461-492 493-500	
10	08/16/00 08/31/00	521-552 553-580	
11	08/16/00 09/25/00	581-612 613-640	
12	08/17/00 09/14/00	641-668 **213-240**	
13	08/17/00	669-700	
Summary is based on the Sponsor's submission dated 12/26/01.			

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Showjien Lee
1/16/02 09:55:41 AM
BIOMETRICS

Mohamed Alosh
1/16/02 10:46:55 AM
BIOMETRICS
Concur with review

Mohammad Huque
1/16/02 11:23:53 AM
BIOMETRICS

APPEARS THIS WAY
ON ORIGINAL